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A. M. A.
Archives of Neurology and Psychiatry

VOLUME 67 APRIL 1952 NUMBER 4

ABRAHAM LINCOLN'S ORGANIC AND EMOTIONAL NEUROSIS

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WADING RIVER, N. Y.

THE PHYSICAL constitution of Abraham Lincoln has perplexed his biographers and portrait sculptors and painters, as it did his personal friends, because of certain enigmatical qualities in his face and personality. More books, articles, and speeches are said to be presented yearly on Lincoln than on any man in history, and his philosophy of democratic government of the people, by the people, and for the people has become the philosophy of the democratic political organization of the United Nations, as well as the United States. It is therefore important that any new evidence on his physical constitution and neuroses that would be helpful in understanding his personality should be published.

The following discussion presents a new consideration of the evidence on his genetic and endocrine constitution, followed by new, recently discovered evidence of an accidental fracture of his skull in childhood from the kick of a horse. This fracture left certain permanent injuries and functional impairments of his brain that greatly influenced the schizoid, melancholic-euphoric development of his personality and thereby his marital life and legal and political career.

HEREDITARY DETERMINATION

Lincoln's face gave evidence of unusual hereditary genetic predispositions in its embryonic development, and hence in the development of his brain and personality. The creases in the skin of the human face are produced principally by the activities of the muscles of the face with attachments to the skin. In most faces, the crease that runs on either side from the nose continues below the cheek and around the upper lip and corner of the mouth, and then passes more or less distinctly around and under the lower lip. In Lincoln's face, as shown by his life mask and photographs, these creases, one on each side, pass from the nose part way only around the upper lip and then turn sharply backward, well above the corners of the mouth. Here they join unusually deep creases that run downward from in front of the cheek bones, between the buccinator muscle of the cheek and the masseter muscle of the jaw, and then curve forward, well back of the mouth, to pass under the chin, where they meet. The expressive effect of this unusual, though not rare, type of facial creasing was enhanced by the length and narrowness of his face. This type of facial creasing is characteristic of the great apes, and when it exists in man it indicates a primitive type of hereditary nervous differentiation.[1]

1. A third cousin, now living, Jonas Basham, whose grandmother, Mimi Hanks, was a first cousin of Lincoln's mother, Nancy Hanks, inherited facial creases remarkably similar to those of Abraham Lincoln, indicating maternal transmission of this unusual characteristic. A genetically oriented genealogical investigation of these, and the hereditary facial characteristics in Lincoln's maternal and paternal ancestry, discussed in this paper would contribute important evidence on his family tree.

Three genetic moles, one on the right side and two on the left side of the face, gave, in relation to these creases, a distinguishing quality to Lincoln's face, which, once seen, was not likely to be forgotten and was, therefore, socially and politically invaluable. The largest and most prominent mole was located on the right side of his face, just above the crease as it turned backward from the upper lip to join the crease lying between the muscles of mastication and the mouth. The mole actually divided the crease, producing a perpetually dimpled, smiling effect on that side of the face. On the left side of the face, one of the other two moles lay on the cheek above the crease where it turned backward from the upper lip, and the other lay lower down on the side of the face, back of the crease, after it joined the masticator-buccinator crease. The positions of these moles in relation to the mole on the right cheek indicate that early in embryonic development, when the head was very small and the face was beginning to form, the right and left moles appeared in symmetrically opposite positions. If this is true, the mole on the left cheek later became divided, and the two parts separated progressively as the muscles and bones of the face enlarged.

Although the psychological effect of these unusual facial characteristics is now unknowable, they gave his face a ready-to-smile set and an unusually comical quality that surely must have reinforced the development of his great sense of humor and propensity to laughter. They probably also combined with other unusual inherited and acquired facial and bodily qualities in reinforcing the formation in his boyhood of the conviction that he was an unusual person, predestined to perform some great mission to be revealed to him, a conviction which developed later into his unique, fixed, lifelong humanitarian inspiration and compulsion.

As an adult, his hair was coarse and black, and his eyes were small, gray, and deeply set. His ears were large, and thick-lobed and extended almost at right angles to his head. His usually long and generally disheveled hair hid this grotesque, comical, inferior feature. His nose was not actually oversized, but it looked large because of his long, thin face. The nostrils did not extend as far into the tip of the nose as in most people, so that the end looked heavy. Lincoln was thought, when young, to be somewhat sensitive about his nose, but not about his ears. He was sometimes ridiculed for being "horse-faced."

HYPOKINETIC CONSTITUTION

Lincoln's body growth and energic constitution show gross evidence of pituitary hyperactivity and gonadal hypoactivity. He was a long, thin baby at birth, with unusually long, thin arms and legs. His body was morphologically like that of his tall, thin mother. She was said by her cousins John Hanks and Dennis Hanks (Hertz [2]) to have been "5 feet 8 inches [173 cm.] high" and to have weighed about 130 lb. (59 kg.), whereas his father was 5 ft. 10 in. (178 cm.) tall and weighed about 190 lb. (86.2 kg.). Lincoln grew to 6 ft. 4 in. (193 cm.) in height and generally weighed less than 180 lb. (81.6 kg.). His legs and arms were disproportionately long for his body, which, when seated, was about the length of an average six-footer.

The skin of his face was weather-beaten, coarse, deeply grained, dark, and generally sallow or muddy. Many years of close exposure in youth before an open

2. Hertz, E.: The Hidden Lincoln, from the Letters and Papers of William H. Herndon, New York, The Viking Press, 1938.

wood fire where he read, possibly left a permanent trophic effect. Deep creases over the forehead, at the outside corners of the eyes and around the mouth indicate an unusual amount of facial work in using the eyes and in laughing.

The neuromuscular tonus of his body was more relaxed than that of the average man. This was shown in the slow, drawling, staccato monotone of his speech; the deliberate, contemplative, meditative manner and slow mental reaction time, and the flat feet. He seems also to have had a lower blood pressure than normal, which probably, when too low, contributed to the production of nervous depression. Self-conscious of his height, he tended to slouch, with stooping of the shoulders and slight bending at the knees; but he generally held his chin up, his posture indicating an ego attitude of humility counterbalanced with well-determined self-reliance and self-respect.

Wold [3] has also reviewed the evidence on Lincoln's physical constitution in relation to his health. He has concluded that any endocrinopathy was limited to indications of thyroid dysfunction, and possibly a slight postpubertal overactivity of the pituitary, which might account for his disproportionately long legs and arms for the rest of the body. Attempts to explain Lincoln's melancholic disposition on an endocrinologic basis would be, Wold says rightly, "merely a venture in the realm of fancy."

However, even though his endocrine constitution is not fully known, it would be more erroneous to disregard the indications of some degree of pituitary, thyroid, and gonadal endocrinopathy than not to consider these factors as having possibly contributed to his hypokinetic constitution.

Many years of hard farm work and wood chopping from childhood to adulthood, out of dire necessity for living, gave him an unusually large and powerful muscular development of the hands and arms, back, and shoulders. His neck, though strong, was long and scrawny in relation to his head and sloping shoulders. His lower jaw was long and heavy and inclined to the acromegalic form.

His constitutional morphologic type was predominantly Kretschmerian asthenic [4] or Sheldonian ectomorphic and cerebrotonic,[5] and his energic constitution was Kempfian hypokinetic.[6] These qualities indicate that Lincoln was probably somewhat hyperpituitary and hypogonadal in endocrine ratio. His constitution disposed to some reduction of autonomic pressure of energy in sexual directions and tended to produce shyness with women and a preference for the company of men, factors of endlessly contributory and determinative influence on the social conditioning and development of his personality.

His slow, drawling speech, slow reaction time, mental deliberateness, and pedestrian rhythm in style of speaking and writing were so consistent with his energic constitution and morphologic type that the latter, obviously, largely determined the former. In Lincoln, the physiopsychological cyclical sequence dominated the psychophysiological cyclical sequence of reactions. In other words, he must be, and gen-

3. Wold, K. C.: Mr. President—How Is Your Health? St. Paul, Bruce Publishing Company, 1948.

4. Kretschmer, E.: Physique and Character, New York, Harcourt, Brace & Company, 1925.

5. Sheldon, W. H.: The Varieties of Human Physique, New York, Harper & Brothers, 1940.

6. Kempf, E. J.: Biological Differentiation of Energic Constitutional Types, M. Rec. **154**:295 (Oct. 15) 1941.

erally was, guided by his feelings in what he said and did, for if they did not support him in the work of fulfilling certain self-commitments he would become miserable, if not melancholic.

LINCOLN'S FACE

If we examine the full-face photographs of Lincoln and the Volk (1860) life mask of his shaven face, we see that the forehead is narrow and high and bulges slightly in the midline. There is an unusual depression in the forehead of the mask,

Fig. 1.—Life mask (Volk)—1860.

with a palpable edge, near the midline above the left eye. This deformation indicates the place of fracture of his skull. His head was said by some of his schoolmates, over 50 years later, to have looked small to them (probably relative to his height). Measurement of the Volk life mask between the bases of the tragi of the ears shows a breadth of 15.3 cm., which is somewhat greater than the breadth of the average head. Hence biographical statements that his head was small are erroneous (Fig. 1).

In his photographs and masks, the left eye is set higher than the right. His left eyebrow is usually elevated more than the right, to help in keeping the upper lid

retracted and the pupil of the left eye exposed. The tendency of the left eye to turn upward left uncovered more of the white surface of the sclera below the iris, giving a slightly staring effect on that side, in strange disharmony with the appearance of the right eye. In the best frontal photograph (Fig. 2) the left eye is definitely out of focus and turned reflexly slightly upward, and possibly outward. This deviation is due to weakening of certain extraocular muscles—possibly the inferior rectus, which is innervated by the third cranial nerve, and/or the superior oblique, which

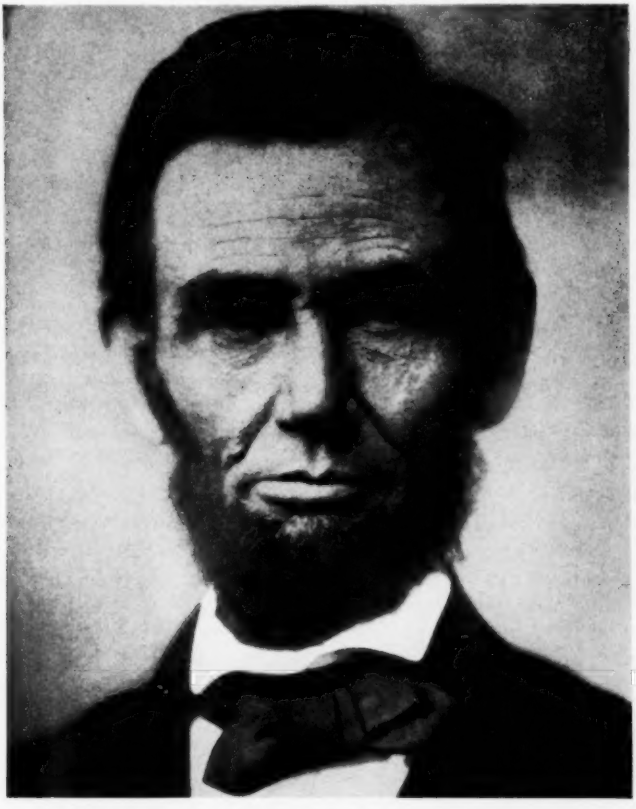

Fig. 2.—Photograph of Lincoln after the Battle of Gettysburg—1863.

is innervated by the fourth cranial nerve. Lincoln's right eye was used dominantly for general vision and no doubt entirely for reading.

Further examination of the face shows that the left half of the upper lip is somewhat thicker than the right half and less expressive, that is, less unvolitionally and volitionally active. Also, the right half of the lower lip protrudes more markedly than the left and is pulled toward the right by the muscles of the cheek. This action characteristically holds the lower lip and facial muscles slightly toward the right.

The right side of the chin is also slightly larger than the left, indicating stronger muscle tonus and development from more active use. The right nasofacial crease, previously described, runs somewhat farther from the midline than the left, and the tip of the nose crooks significantly toward the right. These muscles are supplied by the seventh, or facial, nerve. Although his larynx was large, he had a rasping, high-pitched voice, which grew shrill and squeaky upon emotional excitement, indicating some increase in muscle tonus of the vocal cords or the pharyngeal muscles, under control of the 10th cranial (vagus) nucleus.

Further examination of the life mask, especially measurement for corresponding right and left points from the midline, shows marked differences in the growth of the bones. Although such differences may be genetic or developmental in relation to loss of teeth or defective use from other causes, and cannot be taken as definitely indicative of the effects of an injury of the brain in youth, like the differences in tonic contraction of the ocular and facial muscles, they should be considered and functionally correlated. His cheek bones were unusually high and prominent. The right was larger than the left, and the right orbital ridge and lower jaw were more heavily developed than the left, giving the whole face a decided morphological curve toward the right.

This deformation becomes distinctly visible when the full-face photograph is turned upside down. When the Volk mask is turned upside down, the larger size of the face, the greater prominence of its lip, chin, and lower jaw, and the greater depression of the face under the cheek bone on the right side are striking.

FRACTURE OF SKULL AND INJURY OF BRAIN IN BOYHOOD

All these differences in the development of the facial muscles and bones, and the weakened functioning of the ocular and facial muscles on the left side in particular, indicate that Lincoln suffered a serious injury to his brain before adulthood. The sharp depression in the forehead above the left eye with a definitely palpable edge in the life mask, previously described, shows where his skull had been fractured, and the permanent differences in the nervous tone of the muscles of the two sides indicate that his brain was then permanently injured.

With this conclusion in mind, I searched the history of Lincoln's childhood for evidence of such an accident and found that it occurred in his 10th year. He was driving an unshod horse hitched in a circular mill for grinding corn or sugar cane; and, growing impatient of her slow pace, he shouted, "Get up, you hussy," and gave her a whack with a stick. She kicked back, hitting him in the forehead. He was knocked unconscious for many hours and was thought for a time to be dead. He seems to have recovered without apparent serious after-effects, since he received no special medical attention for the head injury, the doctor living many miles away.[7]

Fracture of the skull and cerebral after-effects were never suspected, or at least never reported, by any of his physicians, although after the age of 30 he consulted

7. H. E. Mock (Skull Fractures and Brain Injuries, Baltimore, Williams & Wilkins Company, 1950) reports that about 7% of untreated fractures of the skull in children end fatally. Before the automobile most such fractures were caused by being kicked in the head.

several for treatment of melancholia and other nervous symptoms.[8] This omission is not surprising, for it was not until after 1890, upon application of x-ray photography, that neurophysiology learned how to explain some of the cerebral effects and nervous consequences of fractures of the skull (Mock[9]).

Ample recording methods now show that an appalling amount of damage to the brain follows blows on the head, at the point of impact and from hydrostatic repercussion (*contrecoup*), through the production of petechial internal hemorrhages, as well as larger subdural blood clots, without external evidence of fracture. Blows on the forehead in boxing have been found to bruise by concussion the frontal lobes of the brain, sometimes with permanent, stupefying, "punch-drunk" effects, without visible injury on the outside of the head.

TENTATIVE DIAGNOSIS OF NATURE OF CEREBRAL INJURY

Although modern neurology requires for diagnosis a far more complete examination of the living subject for positive or negative evidence of nervous impairment, a tentative consideration of several types of injury to the brain that might have produced the unusual complex of symptoms in Lincoln's case, as far as is known, is desirable.

The blow on the forehead over the left eye evidently fractured the skull at the point of impact. The size and depth of the depression are evidence of its severity. It is most likely that a subdural hematoma of considerable size and petechial hemorrhages developed. The left frontal lobe was certainly damaged, which, in a right-handed, right-eyed person, would possibly have some modifying after-effects on the personality. These will be considered later.

The evident, permanent weakness of conjugate movements of the left eye, with the tendency of the eye to turn slightly upward and outward, and the weakness in tonus of the left facial muscles constitute a symptom complex that cannot be satisfactorily explained by a single area of permanent injury to the brain. The lifelong hypertension of the muscles of the pharynx and/or larynx is also indicative of involvement of autonomic nervous action, as are also his daily repetitive moodiness and emotional instability.

Hydrostatic repercussion within the skull on the opposite side (*contrecoup*) might have damaged, by shock or limited subdural hemorrhage, the right cerebral cortex in the lower frontoparietal area, where the weakened muscles have motor representation close together in a small area. But since the facial muscles have bilateral cortical representation, the effects of such an injury in a boy would have been completely compensated for within a few weeks; hence permanent damage must have occurred in some other area.

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8. Lincoln was also struck on the head with a club in a fight with Negro marauders while taking a flatboat down the Mississippi, when he was either 19 or 22. This blow, he said, left a permanent scar (of unknown location). However, it probably did no further damage, for he routed the hoodlums, saved his cargo, and continued the journey.

Congenital injury of the nervous system has also been suggested to account for the ocular and facial symptoms, but this is discredited by the definite history of a blow on the forehead in childhood that knocked him unconscious for many hours.

9. Mock, H. E.: Skull Fractures and Brain Injuries, Baltimore, Williams & Wilkins Company, 1950.

Several small hemorrhages in the midbrain or brain stem might have produced the particular permanent ocular and facial effects. If the nucleus of the left third cranial nerve supplying the inferior rectus muscle were partly damaged, so as to weaken this muscle, the left eye would then tend continuously to turn more or less upward and slightly outward, as shown in Lincoln's photograph, while some degree of volitional coordination would be left. If another spot of hemorrhage damaged the nucleus of the left seventh cranial nerve, the facial muscles on that side would have been permanently weakened. If a third spot touched a certain portion of the midbrain, disturbance of sympathetic nervous action with permanent vocal tension might have followed.

Such weakening of the left facial muscles would probably have only minor secondary effects on the personality.

The production of a high-pitched, rasping voice was more important, but Lincoln largely overcame this professional deficiency by speaking thoughtfully, slowly, and clearly, always with the common-sense intention of expressing himself directly in the simplest words and thoughts that fitted the subject.

Decoordination of the left eye was more serious in that it tended to produce diplopia and severe eyestrain, which was increased upon fatigue or emotional excitement, with the sequelae of headache, nausea, indigestion, and depression. The deformation of facial expression and stress of diplopia required the development of the mental counterdefenses and compensations which characterized his personality.

Lincoln had other symptoms of permanent nervous lesions. With his rasping, high-pitched, nervous voice, he spoke in a slow, staccato monotone, indicating deficiency in sense of inflection in a public speaker, who naturally would have greatly desired this ability.

But most significant of all the symptoms was the repetitive tendency to lapse automatically into a lower conscious state, of mental detachment or abstraction, with characteristic facial expression, described by some of his friends as "ugly and stupid-looking," and by others as "dull," or "sad and abstract," or "detached," or "withdrawn." He told his friends, when a man in the 40's, that he was never without "melancholy." Upon being stimulated by his environment in a way that aroused autonomic-affective reactions of interest, as by some incident or some person's talk, or by reading, his facial expression was observed to change quickly from dull indifference to animated interest, with the tendency to smile and laugh. Herndon, his law partner, said he would sometimes burst out laughing to himself without apparent cause.[2]

Several men and women friends (Mary Owens, W. H. Herndon, L. Swett, and Mrs. Lincoln) saw in him an unusual lack of appreciation of beauty, nicety, and refinement and an inordinate fondness for laughing over vulgar, witty stories with clever, practical, or moral application. In contrast to this kind of aesthetic lapse, he was extremely fond of certain beautiful qualities of prose and poetry and memorized many passages from the Bible, Shakespeare, Burns, Gray, Goldsmith, and other poets. Most of all, he was highly conscientious about being truthful, reliable, honest, kind, fair, just, and loyal. His sense of fitness in the clarity and logic of his statements, his discrimination of innocence and guilt, truth and deception and justice in the courtroom, and his sense of definition and appropriateness in his

speeches, were masterly. These aesthetic contrasts, of deficiency in some respects and of supremacy in others, might have been the effects of cultural preference more than of cerebral capacity.

The continuous tendency to lapse into melancholy or gloomy "blues" was, however, probably consistent with a permanent, cerebrally initiated, schizoid tendency to lapse automatically into a mentally dull, detached, drowsy state, and then to react, upon interpersonal stimulation, with excessive euphoric compensations.

This inhibitory-reaction tendency was also relatively overcome by the culture of certain forms of self-excitation, such as reading aloud to himself or other people, telling humorous stories, and becoming particularly adept in engaging in legal fights for justice. He liked to read aloud, he said to Herndon,[10] for thereby he gained the benefit of hearing, as well as seeing, what he read and remembered it more easily.

Two different loci of cerebral injury might have produced the complex volitional mental instabilities with the unstable sympathetic nervous reactions under stress or fatigue. One such locus would be a subcortical disruption (thalamic-sensory or hypothalamic-motor) at the head of the autonomic nervous system that depressed sympathetic nervous action and tended to produce dulness or drowsiness upon lack of excitatory stimulation. The other would be an impairment of the frontal cortex on the left side (of a right-eyed and right-handed person), involving the cortico-thalamic cycle of nerve impulses, that reduced the volitional production of the conscious stream of visual imagery of self-in-its-environment, so that such a person would require more external stimulation than would a normal one in order to remain mentally attentive. A person with this type of cerebral lesion, in order to keep mentally alert, would have to be involved, or keep himself involved, in emotionally stimulating situations by cultivating special stimulating interests and objectives, such as a passion for legal justice for all people. Lincoln did just this, as a humorist seeking happiness and as a humanist seeking justice, in an endless fight to overcome the tendency to lapse into a rut of sad, gloomy, suicidal preoccupations.

DIPLOPIA AND ASTIGMATISM

The earliest evidence of Lincoln's visual decoordination has been recorded by Shastid,[11] as told to him by his father, Dr. Shastid, an oculist who practiced in Pittsfield, Ill. The elder Dr. Shastid, when a boy, lived in New Salem and knew Abe Lincoln, then in his mid-twenties, as the storekeeper and postmaster of the town. He described him as a melancholy but kindly spoken person, who liked to amuse children, as well as grown-ups. Abe would sit on a box in front of the store when not waiting on a customer, generally with a dejected and abstracted expression. He would sometimes lie on the ground near the store, with his bare feet elevated against the trunk of a tree, and read. Shastid noticed that Lincoln's left eye looked queer at times and would suddenly get crossed and turn upward.

Some 20 years later, when a physician and oculist, Shastid saw Lincoln in several debates with Douglas and in several trials in court as a lawyer. He then recognized the ocular condition as hyperphoria from a certain weakness of the muscles of the left eye, which continuously caused the eyeball to turn upward. Upon

10. Herndon, W. H., and Weik, J. W.: Herndon's Lincoln: The True Story of a Great Life, Chicago, Belford, Clarke, & Company, 1889.

11. Shastid, T. H.: My Father Knew Lincoln, Nation **2**:227, 1929.

excitement this condition would suddenly increase and produce a severe cross-eyed effect. Dr. Shastid suggested that the hyperphoria caused intense eyestrain and uneasiness and was at least partly the cause of Lincoln's moodiness or "chronic inexpressible blues." He thought that Lincoln possibly was also color-blind, for Lincoln once said to his (Shastid's) mother, when she showed him her flower garden, that flowers and sunsets had no beauty for him, as they did for other people.

Lincoln's right eye was dominant and was always used for vision, while the tendency of the left eye to turn upward and outward produced more or less overlapping of visual images. Like most such persons whose diplopia begins in youth, he soon adapted to this condition by reacting attentively to the imagery that he saw more clearly, that is, the image of the right eye, while ignoring what the left eye saw. This required more or less volitional brain work, which was carried on easily enough until manhood, when at times mental visual fatigue or emotional strain became too severe.

Through the adult years Lincoln had many nervous attacks, characterized by eyestrain, headache with nausea, and indigestion, so severe that he often became unable to work and had to lie down with a cold compress over his eyes. He had couches in his law office, at home, and in the White House for this purpose.

Probably in youth and maturity Lincoln was unable to focus both eyes for any length of time without volitional effort. Herein existed an unconscious, self-protective influence on conscious learning. He must not only use right-eyed instead of left-eyed vision, but he must consciously and conscientiously see mentally the right side and better side of things in order to reduce the emotional strain of being wrong. His highly persistent work in developing a clear thinking, logically visualizing, auditizing, and verbalizing mind counteracted the mentally befuddling effects of diplopia and protected him against the tendency toward gloomy mental visualizing.

In 1857, at the age of 48, while shopping in a jewelry store, he bought, upon the recommendation of a friend, his first pair of "spectacles" for reading. He tried on several pairs and paid 37½ cents for the glasses that he read best with. Until a few years before he had probably normal vision and effective accommodation of the right eye, although the accommodation was always attended by more or less strain from decoordination of the left eye.

The following reports on Lincoln's eyes and glasses are taken from several later authoritative sources. The glasses were reported by Almer Coe, of Chicago, to have in each lens the strength of +6.75 D. This indicated that Lincoln probably had 4 or 4½ D. of hypermetropia, or farsightedness, at the age of 48. This severe disability had no doubt been developing for a number of years and required constant effort to produce sufficient accommodation for reading.

Dr. W. H. Crisp,[12] an ophthalmologist, recorded the following observations: Full-face photographs show an upward deviation of the left eye, great enough to produce a lack of fusion of its images with those of the right eye. The two eyes did not work together, possibly as a result of a vertical strabismus of the left eye.

Dr. S. Mitchell[13] found evidence of left hyperphoria and hypertropia and suggested that the corrugations of his brow and the crow's-feet at the corners of the

12. Crisp, W. H.: The Eyes of Abraham Lincoln, Am. J. Ophth. **15**:775, 1932.

13. Mitchell, S.: Diagnosis of Heterophoria from a Portrait, Ophth. Rec. **23**:224 (May) 1914; cited by Wold.[8]

eyes showed that Lincoln habitually used auxiliary facial muscles to support the external muscles of the eyes in the work of visual coordination.

Dr. K. C. Wold [3] suggested that the diplopia was caused by a decoordination of the external muscles of the left eye, which was inherently connected in some way with the other facial asymmetries.

No physician on record, so far as I know, has attempted to explain the origin and nature of the asymmetrical functioning of the facial and ocular muscles on the left side, although some have discussed the nervous effects of eyestrain.

All the known symptoms are grossly explainable, I think, as the result of a cerebral injury attending the fracture of his skull in boyhood, and producing permanent, specific forms of nervous decoordination (organic neurosis).

PRACTICAL ADAPTATION TO GLOOMY EYESTRAIN

The continuous tendency to visual decoordination was sufficient to increase nervous fatigue and depression of mood or "spirit" upon prolonged use of the eyes, particularly for reading. Such conditions tend in most youths to induce discouragement of reading, lethargy with laziness, and a preference for reading from a reclining position to ease the eyestrain. Despite his impairment, Lincoln was an eager student and liked to lie on the floor and read aloud by the light of the open wood fire. Later, as a man, he often read in a reclining position on a couch or on the floor and preferred to read aloud.

We have additional evidence of how Lincoln's neurovisual difficulties influenced him in everyday life. His work as a lawyer and politician required him to read excessively. He adapted to this by learning to scan pages rapidly for essentials and by developing a highly retentive memory. When it was unnecessary to use his eyes or mind, he would lapse into his characteristic semiwithdrawn mental state, previously described.

ENIGMATICAL EXPRESSION

The right side of Lincoln's face was animated and emotionally expressive, whereas the left side functioned more weakly, looked duller, and was out of harmony. The meaning of the duality and changes in his facial expression baffled everyone. Strangers, who estimated the man by his dull, perplexed face and sad, tired eyes, were always astonished at the quick change of his expression to alertness when he became interested in their conversation and wanted to make some contribution to it. Many strangers, including lawyers, generals, and members of his cabinet, upon first acquaintance, thought themselves superior to this ugly, dull, sad, weak-looking man, only to find themselves amazed and mastered by the ready wit, common sense, logical intelligence, and strength of character that became evident upon his being required to look out for himself.

As his law partner from 1843 to 1861, Herndon was no doubt the most frequent, intimate, and interested observer of Lincoln's personality and physical constitution day after day. He [10] has stated that Lincoln's most marked and persistent characteristic was a predisposition to become melancholy or sad and depressed. This attitude showed in his facial expression when he was sitting alone or when he was in a group and not taking an active interest in the conversation. Many other intimate friends of Lincoln were similarly impressed, as recorded in various biogra-

phies. Some of his friends thought, because of the muddy, leathery condition of his skin, that this facial lapse was due to indigestion and insufficient secretion of bile.

Herndon imagined that the morbidity was caused by some "occult" condition, which could not be explained by observation or reasoning. It was "ingrained," he said,[2] and "could not be reduced to rules or the cause assigned. . . . It was necessarily hereditary. . . . It was a part of his nature and could no more be shaken off than he could part with his brains. Simple in carriage or bearing, free from pomp or display, serious, unaffected, Lincoln was a sad looking man whose melancholy dripped from him as he walked." Herndon observed that "the look of sadness was more or less accentuated by a peculiarity of one eye (left), the pupil of which had a tendency to turn or roll slightly toward the upper lid, whereas the other one maintained its normal position equidistant between the upper and the lower lids." He also noticed that the tip of Lincoln's nose and his mouth turned toward the right. "Mr. Lincoln was a peculiar, mysterious man—had a double consciousness, a double life. The two states, never in the normal man, co-exist in equal and vigorous activities though they succeed each other quickly. One state predominates and, while it so rules, the other state is somewhat quiescent, shadowy, yet living, a real thing. This is the sole reason why Mr. Lincoln so quickly passed from one state of consciousness to another and different state" (letter from Herndon to J. Weik, Feb. 2, 1891, Hertz [2]).

Josiah Crawford (Herndon and Weik [10]) remembered that as Lincoln became occupied with reading, his lower lip stuck out. This, he thought, was only a lifelong "habit." Actually, as his mask (1860) and photographs show, the right half of the lower lip always protruded more than the left half and was pulled with the other muscles of the mouth slightly to the right side. When he was reading quietly or thinking actively, the degree of dominance in neuromuscular activity of the right side of his face tended generally to increase. When he was mentally inattentive, the lack of nervous stimulation tended to let the right side of his face decrease in activity faster than the relatively hypotonic left side, giving his expression a perplexed quality, which was misunderstood by those who would read his face.

SUPERSTITIOUS INTERPRETATION OF DIPLOPIA

Most persons with hyperphoria learn to disregard the dimmer, overlapping visual image without being conscious of such work. However, when eyestrain and fatigue or emotional excitement grow excessive, the visual decoordination increases until the two more or less distinct images tend to be seen with increasing mental confusion and uneasiness. Lincoln learned to cultivate a calm, humorous, kindly attitude, happy interpersonal relations, and a common-sense philosophy of life, which generally protected him from emotional provocation and increase of this distress. Yet he needed to have certain qualities of sympathetic excitation in order to maintain his best working pressure.

His description of a particular experience shows how he mystically interpreted his first experience with complete diplopia. Upon learning of his nomination for the presidency, in 1860, by the national convention of the young Republican party, Mr. Lincoln returned to his home, after a strenuous day, tired and nervous, and lay down on a couch in his wife's sitting room to rest. Directly across the room,

facing him, was a large mirror on the bureau. In it he saw for the first time a double image of his face, and it perplexed him greatly. He described the experience as follows:

> As I reclined, my eyes fell upon the glass, and I saw distinctly two images of myself, exactly alike, except that one was a little paler than the other. I arose and lay down with the same result. It made me feel quite uncomfortable for a few minutes, but, some friends coming in, the matter passed from my mind. The next day while walking the street, I was suddenly reminded of the circumstance, and the disagreeable sensation produced by it returned. I had never seen anything of the kind before, and did not know what to make of it. I determined to go home and place myself in the same position, and, if the same effect was produced, I would make up my mind that it was the natural result of some refraction or optics, which I did not understand, and dismiss it. I tried the experiment with the same result; and, as I had said to myself, accounted for it on some principle unknown to me, and it ceased to trouble me. 'But the God who works through the laws of Nature might surely give a sign to me, if one of his chosen servants, even through the operation of a principle in optics.

Lincoln had been a devoted reader of the Bible since boyhood and superstitiously believed, as it taught by numerous episodes in many chapters, that God revealed his wishes and commands to chosen people by natural and occult signs, such as visions, voices, and dreams, as well as by the feelings of the heart and conscience. He said that he felt himself "to be aided and enlightened by One who is stronger and wiser than all others."

Lincoln's comments on his first experience with complete diplopia, as a double visual image of his face in a mirror, shows that, while he regarded it with common sense, it also excited him superstitiously, mystically, religiously, and wishfully. He hoped somehow to receive an inspiring sign, as a chosen servant of the people and of God, to think of a way of solving the violent conflict between the free and the slave states that would be acceptable to both sides and eventuate in the peaceful preservation of the Union. By his form of thought, feeling, belief, and faith in having received a definite sign and divine inspiration, he was able to maintain high, consistent integrity of purpose against the subconscious tendency to schizoid indecision and confusion.

He did not really dismiss this double vision of his face as being caused by a law of optics that he did not understand. It continued to mystify him, and he often thought of it. When he was President, after a dream, a few days before his assassination, in which he saw himself dead in state in the White House, he confided to Ward Lamon how he finally interpreted its premonitional meaning for his destiny. He would have two terms as President, and in the second term he would be killed.[14]

PREFERENCE FOR PHOTOGRAPHS OF RIGHT SIDE OF FACE

The collected photographs of Lincoln published by Frederick Hill Meserve and Carl Sandburg,[15] and by Stefan Lorant,[16] show that in many of them he has a similar serious, solemn, dignified, unsmiling but kindly, reposeful, mentally inactive facial expression. In a few, the face is so moody, depressed, and unusually per-

14. Lamon, W. H.: The Life of Abraham Lincoln, from His Birth to His Inauguration as President, Boston, Osgood & Co., 1872.

15. Meserve, F. H., and Sandburg, C.: Photographs of Abraham Lincoln, New York, Harcourt, Brace & Company, 1944.

16. Lorant, S.: Lincoln; His Life in Photographs, New York, Duell, Sloan & Pearce, Inc., 1941.

plexed, and the eyestrain so pronounced, that many people doubt whether they are authentic reproductions. Not until one examines the lines of the eyes, mouth, and skin closely in such photographs is the identity fully established.

Lincoln's usual facial expression, when not being photographed, was that of patient humility, kindness and naturalness of attitude, honesty, simplicity, and serenity of thought, with the tendency to smile pleasantly or to burst into a good-humored laugh. His face also showed great self-reliance, courage, and firmness, with thoroughgoing dignity and repose, when he was not tending to lapse into dull conscious detachment. The left side of his face, being less mobile and not in completely harmonious affective tone with the right, and contributing less volitional kinesthesis to his brain, was less truly representative of his state of mind.

The differences in expression seem to have influenced Lincoln, or his photographers, to prefer photographs of the right side of his face, since most photographs were taken from the right quarter or the profile. Only a few were taken from the left side or from the front. Although a great laugher, he tended to keep his mouth closed firmly, with more protrusion of the right lower lip than of the left when being photographed. Even though Mrs. Lincoln chided him for persisting in looking too solemn, he could not be persuaded to smile freely before the camera. Herndon said that from the moment Lincoln faced the camera his face would grow serious and sad.[2]

Lincoln's face was completely shaven until, in his campaign for the Presidency in 1860, he was persuaded to grow a beard. The numerous changes in the style of cutting his beard and hair indicate that he and his barbers or Mrs. Lincoln indulged in no little experimentation for the best effect. His photographs show they tried a number of different trimmings, with one constant feature, namely, shaving the upper lip, lower lip, and upper half of the chin, while letting a beard grow on the lower half of the chin and throat and the sides of his face. The coarse, black hair on his head was generally cut so as to remain unusually long, probably for reducing the prominence of his ears. He liked to play with his hair and parted it on either the right or the left side, as he fancied. Its generally disheveled appearance indicates that he habitually, self-consciously mussed it with his fingers.

VICIOUS CIRCLE OF ORGANIC AND EMOTIONAL NEUROSES

The nausea and headaches from exacerbation of such continuous malfunctioning of the eyes are not uncommonly attended by a depressed, dark, gloomy outlook on life. Many ophthalmologists hold on physiopsychologic grounds that the mental state follows from the physical condition, constituting primarily an organic neurosis. Most psychiatrists hold that, although such organic causes of visual malfunction tend to increase headaches and depression upon mental fatigue and emotional discouragement or excitement, the tendency to visual decoordination is psychopathologically increased by internal mental conflict and emotional depression or excitement, with the formation of a progressive vicious circle. Abundant evidence from the biographical study of Lincoln shows that the organic and emotional neuroses formed a vicious circle and worked pathologically, daily throughout his life, and that he cultivated a common-sense attitude to protect himself from himself and his personal relationships that was largely successful but not infrequently broke down.

It is impossible to understand the effects on the development of Lincoln's personality of the injury to his brain in childhood without considering their connec-

tions with the conditioning influences of the different members of his family and his social and professional relationships. Conversely, we cannot estimate soundly his personal adjustments to the great crises of his life without correlating them with the organic factors in his neurosis. The thousands of biographical studies and estimations of Lincoln in books, papers, editorials, and speeches published since his death have largely been based on a fundamental misunderstanding of the determining factors in the development of the man's personality and his great motives, although many have estimated ably the part he played in history.

The studies of Lincoln's facial expression made by physicians have related it to his ocular symptoms only as an auxiliary effort to control vision. The permanently destructive effects on his brain by the accident in boyhood, as the cause of his visual, facial, and vocal impairment and melancholic detachment, have been entirely overlooked. Of course, the definite history of the accident and the dent in his forehead discredit the theory of cerebral injury at birth or of hereditary factors as the cause. A biography will be published soon giving special attention to the interactions of his organic and emotional neuroses with the origin and development of his great inspirations, leading up to and including his Presidency. It will show for the first time how the cerebral injury and family environment in boyhood influenced the development of his personality and mental convictions as a man.

Because of limited space, it must suffice here to add the well-known fact that Lincoln (born and raised in a wilderness log cabin) had an unusually attractive, intelligent, heroic, although semiliterate mother, to whom he was greatly attached in childhood. She died tragically of an epidemic fever when he was 9 years old, and his father married again when he was 10. His stepmother, an unusually intelligent pioneer woman, was very kind and devoted to her stepson and encouraged him to learn to read and write and to educate himself. He always retained a persistent, gloomy mother fixation, with interest in melancholy and tragic songs and poetry about the dead and the past.

His betrothed, Ann Rutledge, died in 1837 of an epidemic fever, and he reacted with suicidal melancholia, which lasted for several months. The following year he courted Mary Owens and proposed marriage but was unable to complete this obligation because of conflicting emotional revulsions against it.

In 1840 he courted Mary Todd, and suffered such intense schizoid depression that he was unable to appear for the wedding ceremony. He again became melancholic, incoherent, and suicidal but recovered sufficiently in a few weeks to return to his office. He married Mary Todd in 1842; but, although she had four sons by him, he was never able to love her. He continued to have repeated attacks of emotional nervousness, with headaches and indigestion, for the rest of his life, particularly when forced to endure some grave political or military frustration.

Abraham Lincoln, throughout his maturity, until his death, was never free for a day from the tendency to melancholy from the combined interactions of an organic visual neurosis and a specifically conditioned, emotional neurosis that worked in a repetitive, vacillating, vicious circle, against the miserable effects of which he protected himself by cultivating a practical, common-sense philosophy of humanism and humor.

CHRONIC PSYCHOGENIC HYPERVENTILATION

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WE HAVE been greatly impressed by the frequency with which the acute hyperventilation syndrome has been encountered in our psychosomatic clinic.[1] This frequency has been pointed out by others,[2] and there are many excellent discussions of the clinical features and pathological physiology.[3]

In the usual case of hyperventilation the condition occurs as a discrete episode, usually of a few minutes' duration, recurring nearly always in a situation of great emotional or physical stress, and usually part of a generalized personality dysfunction, chiefly anxiety neurosis or hysteria.[4] Patients with this disorder overbreathe for short periods of time, during which they are aware of dyspnea, chest discomfort, palpitation, lightheadedness, paresthesias, and, finally in some, syncope or tetany. All these symptoms tend to increase the patient's panic and potentiate the hyperventilation.

Although these short episodes of hyperventilation may recur frequently and become alarming to the patient, long-continued overbreathing on a psychogenic basis is only rarely encountered. To hyperventilate continually, the patient must respire in the presence of a greatly decreased chemical stimulus (pressure of carbon dioxide [pCO_2]) to the respiratory center, and in spite of respiratory muscle fatigue, discomfort, and alkalosis.

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1. Saslow, G.: An Experiment with Comprehensive Medicine, Psychosom. Med. **10**:165, 1948.

2. Rice, R. L.: Symptom Patterns of the Hyperventilation Syndrome, Am. J. Med. **8**:691, 1950. McKell, T. E., and Sullivan, A. J.: The Hyperventilation Syndrome in Gastroenterology, Gastroenterology **9**:6, 1947.

3. Kerr, W. J.; Dalton, J. W., and Gliebe, P. A.: Some Physical Phenomena Associated with the Anxiety States and Their Relation to Hyperventilation, Ann. Int. Med. **11**:961, 1937. Engel, G. L.; Ferris, E. B., and Logan, M.: Hyperventilation: Analysis of Clinical Symptomatology, ibid. **27**:683, 1947. Soley, M. H., and Shock, N. W.: Etiology of the Effort Syndrome, Am. J. M. Sc. **196**:840, 1938.

4. We use the term hysteria as defined by Purtell and associates (Purtell, J. J.; Robins, E., and Cohen, M. E.: Observations on the Clinical Aspect of Hysteria, J. A. M. A. **146**:902 [July 7] 1951).

We have recently had the opportunity to study a patient with chronic hyperventilation. Because of the paucity of reported cases this case is being presented in detail.

REPORT OF A CASE

Mr. H., a white man aged 66, married, a small-loans business man, was admitted to Barnes Hospital for the second time on Sept. 30, 1950, with the complaint of shortness of breath.

The first hospitalization, in the spring of 1945, when he underwent a one-stage suprapubic prostatectomy for benign hypertrophy of the prostate, was uneventful. He was apparently in good health until the onset of his present illness.

He stated that this began approximately eight months prior to his admission, at which time, while painting some shelves at shoulder height, he suddenly had a vague feeling of illness and was forced to lie down. Though he had no chest pain, palpitation, or dyspnea, he immediately suspected heart disease. Shortly after this experience, immediately after sexual intercourse with a woman other than his wife, he experienced severe dyspnea and palpitation. He became very frightened. He vowed never to indulge in sexual intercourse again, and for the week following he was entirely asymptomatic. One week later, however, he again had sexual intercourse with the same woman and again experienced the severe, frightening dyspnea and palpitation. After this he abstained from all sexual activity, despite the fact that he had been carrying on a series of love affairs, more or less continuously, for the past 45 years.

A few weeks later, while trying to chop a small wooden box into kindling, he had a third, severe attack of dyspnea, palpitation, faintness, and dizziness. He felt forced to retire to bed and called his family physician. The latter made a diagnosis of heart disease and kept the patient at bed rest for five or six months. Despite bed rest, dietary measures, and digitalization, he continued to experience nearly continuous dyspnea, with occasional palpitation. He finally decided to come to St. Louis for consultation with a cardiologist, who hospitalized him.

Physical Status on Admission.—The temperature was 37.9 C., the pulse rate, 96; the respiration rate, 22, and the blood pressure, 160/100.

The patient was a short, fairly well-developed, well-preserved man, who looked younger than his stated age (66) and who was obviously dyspneic. He had a few café-au-lait spots over his back and slight cyanosis of the lips. The anterior-posterior diameter of the chest was moderately increased. The lungs were clear. The heart did not appear enlarged on percussion. There was a normal sinus rhythm. The sounds were of good quality, and no murmurs were heard. The edge of the liver was just palpable under the right costal margin. There was no edema. The remainder of the physical examination revealed nothing remarkable.

Initial Laboratory Data.—The red blood cell count was 4,680,000, and the hemoglobin content was 14.8 gm. per 100 cc. Other initial laboratory data, including the white blood cell and differential counts, results of urinalysis and stool examination, serological reaction for syphilis, blood nonprotein nitrogen, fasting blood sugar, and blood cholesterol, were also within normal limits. The venous pressure was measured on three occasions, soon after admission, and was found to be 148, 110, and 115 mm. of water, respectively. The corresponding circulation times, determined with dehydrocholic acid (decholin®), were 25, 29, and 30 seconds. Further studies of circulation time, with other substances, were as follows: ether, 9 seconds; saccharin, 29 seconds; fluorescein (arm-to-histamine wheal on opposite arm), 26 seconds (normal, 10 to 16 seconds).

A roentgenogram of the chest showed an enlarged heart, an elongated, tortuous aorta, and calcific nodules in the left perihilar region. The cardiac enlargement was principally in the region of the left ventricle. The basal metabolic rates were + 14 and + 20% on two occasions, and electrocardiograms showed an abnormal form of the ventricular complex with indications of left ventricular enlargement and premature ventricular contractions in a horizontal heart. The abnormalities consisted of an inverted T wave in Leads I and II, $_{a}V_{L}$, V_3, V_4, V_5, and V_6, with an amplitude of the QRS complex in lead $_{a}V_{L}$ of + 19 mm.

Initial Impression.—The patient was thought to have hypertensive cardiovascular disease with cardiac enlargement and failure of the left ventricle, associated with some emphysema.

However, the peculiar way in which the patient breathed, described as "breathing like a fish," and the fact that he would lie flat on his back to obtain relief from the distressing dyspnea of the upright position were disturbing features.

Though there was some doubt as to the presence of decompensation, as a therapeutic trial the patient was placed on a low-salt diet, digitalized with digilanid* (a mixture of the isomorphous cardioactive glycosides lanoside A, lanoside B, and lanoside C), and given an injection of a mercurial diuretic. Despite these measures, there was no change in his symptoms, weight, physical findings, or circulation time. He was therefore referred to the Laboratory of Thoracic Physiology and to the Division of Psychosomatic Medicine for further study.

TABLE 1.—*Analysis of Pulmonary Volume and Carbon-Dioxide Content, pH, and Electrolyte Content of Arterial Blood*

	Ventilation				Arterial Plasma		Arterial Blood			
Date	Tidal Volume (Cc., BTPS*)	Rate/ Min.	Effective Alveolar Ventilation	Respiratory Quotient	CO_2 (mM./L.)	pH	pCO_2 (Mm. Hg)	CO_2 (mM./L.)	Oxygen Saturation (%)	Buffer Base (mEq./L.)
Oct. 6	1,159	16	16.6	1.13	23.4	7.58	25.0	18.0	91.9	50
Oct. 10	966	20	16.92	0.88	23.7	7.58	25.2	19.6	95.4	50
Oct. 11										
a. m.	950	20	16.6	0.92	24.2	7.55	27.0	19.3	98.5	50
p. m.		Quiet		....	27.6	7.51	34.0	....	....	..

* BTPS, at body temperature and pressure, saturated with water.

TABLE 2.—*Arterial Plasma Electrolytes (mEq./L.)*

Date	HCO_3	Cl	Protein	Na	K	Ca	pH
Oct. 11, a. m.	24.0	116.0	14.3	142.1	4.2	2.8	7.55
Oct. 11, p. m.	26.4	111.3	13.6	143.2	4.5	3.2	7.51

TABLE 3.—*Lung Volume and Subdivisions**

	(BTPS †)
Total volume	4,911 cc.
Vital capacity	3,079 cc.
Tidal volume	700 cc.
Inspiratory capacity	2,680 cc.
Expiratory reserve	399 cc.
Residual volume	2,231 cc.
Residual: total volume	41.9 %
Alveolar nitrogen after 7 min. of oxygen breathing	1.41 %

* According to terminology in Definition and Symbols in Respiratory Physiology, Federation Proc. **9**: 602 (Sept.) 1950.

† BTPS, at body temperature and pressure, saturated with water.

Additional Studies.—Respiratory studies included determination of total pulmonary volume and its subdivisions. Samples of arterial blood were drawn anaerobically on four occasions and analyzed for carbon dioxide content,[5] pH,[6] and electrolytes.[7] The results of all these determinations are presented in Tables 1 to 3.

5. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry; Methods, Vol. II, Baltimore, Williams & Wilkins Company, 1932.

6. Van Slyke, D. D.; Weisiger, J. R., and Van Slyke, K. K.: Photometric Measurements of Plasma pH, J. Biol. Chem. **179**:743, 1949.

7. Weichselbaum, T. E., and Varney, P. L.: A New Method of Flame Photometry, Proc. Soc. Exper. Biol. & Med. **71**:570, 1949. Dr. Weichselbaum made the flame photometric determinations of the plasma electrolytes.

A more detailed history revealed that the patient considered himself a steady, calm, worry-free person, whose motto was, "If something is wrong, correct it if you can; forget it if you can't." However, he revealed certain information that raised doubts as to how successfully he had lived up to his philosophy. Instead of being "happy-go-lucky" and care-free, the patient admitted great concern with keeping himself healthy and in good physical condition. To this end, he avoided tobacco, alcohol, coffee, tea, etc., and he spoke of these precautions with obvious pride. He was overly anxious to assure us that he would religiously carry out the physician's orders. He was so emphatic concerning this matter that it was felt not to be in keeping with the philosophy of a man who had stated that he was not afraid to die. As an example, he stated that if his doctor told him to avoid salt, "they could place 90 salt shakers on my tray, and I wouldn't touch one." Though he denied any fear of heart disease, he told of many episodes in the past when he had felt indisposed, and, without any cardiorespiratory symptoms whatsoever, had immediately suspected heart disease. On the other hand, he remembered an episode that had occurred about 15 years before during which he experienced sudden, severe, but temporary, palpitation, dyspnea, and chest pain. He was sure it was his "heart," but he did not consult a physician. Soon thereafter, he arranged his business in such a way that he spent half the year vacationing in Florida. When at home, he seldom worked more than a few hours a week. He denied any fear of heart disease as motivation for this change, but he could give no other reasonable explanation. Despite these denials, he admitted heart consciousness, and he daily checked his pulse. This history suggested that the patient was suffering from a moderately severe anxiety neurosis with considerable concern about the state of his heart.

In a review of the patient's history to discover any possible factors which might explain his preoccupation with heart disease, it was learned that the patient's father died suddenly of heart disease when the patient was 17 and living with him. No further details were known about this. In addition, within the past 10 years two men in the patient's home town had died during, or immediately after, intercourse with women other than their wives.

The examiner, on entering the patient's room, noted that he was lying perfectly flat in bed, with no pillow, and that he was breathing chiefly through his mouth, "like a fish." On the basis of the history and observation of the patient, it was concluded that his symptoms were chiefly due to hyperventilation. As a test of this hypothesis, the patient was instructed to walk up and down the hospital corridor to the point of unbearable dyspnea (he had complained of this previously). At the point of maximal dyspnea, the patient was made to rebreathe into a paper bag. Instead of finding this impossible after a few seconds, as would be expected in cardiac failure with dyspnea, the patient found the rebreathing quite comfortable, and his respirations gradually decreased and became normal.

It was suggested to the patient that his symptoms were not due to his actual heart disease, but were related to his fears of heart disease and death. He rejected any such explanation, refused psychotherapy, and was discharged, after having been instructed in several simple measures designed to forestall overbreathing. A letter received from him while he was sojourning in Florida, two months later, stated that his "breathing almost suddenly became practically normal about two weeks after his discharge."

COMMENT

From a reconstruction of this case, it is quite apparent that the patient was suffering from a moderately severe, though masked, cardiac neurosis. Superimposed upon this, there developed hypertensive cardiovascular disease with cardiac enlargement, and probably some significant encroachment upon cardiac reserve. This was manifested, under the physical and emotional strain of sexual intercourse, by the appearance of unusual dyspnea. This episode recalled all his fears of heart disease and the dyspnea probably was reinforced by the stories of cardiac death under similar circumstances that he had heard of previously. It was at this time that he began to hyperventilate. A repetition of this series of events a week later and the symptoms resulting from the chopping of wood were enough to establish the

hyperventilation as a more or less chronic, though intermittent, symptom complex. His physician's diagnosis and treatment then served to entrench the pattern more firmly.

Though the patient refused any psychotherapy, he has apparently recovered from his distressing symptoms. We have noted that many of our patients can be entirely relieved of symptoms by appropriate instructions without resort to psychotherapy. The latter can follow amelioration of symptoms and be directed against the underlying personality disturbance which is frequently present.

We have found that it is of great help to instruct the patient to stop and take note of his breathing frequently during the day, especially under conditions that usually upset him. It is most advantageous for his family, friends, and co-workers to help him with this. Then, when overbreathing begins, it is very useful for the patient to carry out some purposeful activity, such as whistling, singing, or reciting, during which a controlled respiration is necessary. These measures will eliminate symptoms in a high proportion of patients. Rebreathing into a paper bag will abort the full-blown picture once the overbreathing is begun and cannot be stopped willfully. It is noteworthy that once this pattern of breathing has been interrupted, it seems not to recur.

Physiologic studies of patients during long-continued hyperventilation are not numerous in the literature. Overbreathing during encephalitis was studied by Harrop and Loeb [8] in 1923, and by Peters and associates [9] in 1926. Both groups of investigators found that their patients had acquired severe respiratory alkalosis. The only report of chronic hyperventilation on a psychogenic basis that we find in the literature is that of Talbott, Cobb, and others.[10] Their (female) patient, suffering from hysteria, had a great enough alveolar ventilation to lower the carbon-dioxide pressure to 15.8 mm. Hg and to increase the pH to as much as 7.57. Quiet respiration under hypnosis brought these changes nearer to normal, without abolishing them completely.

In our patient the total lung volume and its subdivisions (Table 3) were within normal limits except for a small increase in the ratio of the residual to the total volume. Functionally, then, there was no significant emphysema. Effective alveolar ventilation, with an arbitrary 120 cc. of dead space, was about 17 liters per minute on the three occasions on which it was measured (normal, approximately 5 liters a minute). This increase in ventilation was due chiefly to the large volume of tidal air, a mechanism common to the usual episodic hyperventilation syndrome. Talbott's patient, however, hyperventilated by a marked increase in rate.

As a direct result of this increased ventilation, carbon dioxide is washed out of the alveoli and out of the perfusing blood as it comes into equilibrium with the air across the alveolar membrane. This primary reduction in carbon-dioxide pres-

8. Harrop, G. A., and Loeb, R. F.: Uncompensated Alkalosis in Encephalitis, J. A. M. A. **81**:452 (Aug. 11) 1923.

9. Peters, J. P.; Bulger, H. A.; Eisenman, A. J., and Lee, E.: Total and Base Equilibrium of Plasma in Health and Disease: IV. The Effects of Stasis, Exercise, Hyperpnea and Anoxemia, and Causes of Tetany, J. Biol. Chem. **67**:176, 1926.

10. Talbott, J. J.; Cobb, S.; Coombs, F. S.; Cohen, M. E., and Consolazio, W. V.: Acid-Base Balance of the Blood in a Patient with Hysterical Hyperventilation, Arch. Neurol. & Psychiat. **39**:973 (May) 1938.

sure and the resulting lowered carbon-dioxide content of the plasma and the increased pH of the arterial blood are shown in Table 1. Similar changes have been observed by Grant and Goldman [11] and by Shock and Hastings [12] in normal persons who hyperventilated for short periods, and by Talbott and associates,[10] Harrop and Loeb,[8] and Peters and associates [9] in patients with chronic hyperventilation. In our patient, the afternoon sample of Oct. 11 was drawn after quiet respiration, which had been established by rest, distraction, and partial hypnosis for 30 minutes. Even this short reversion to quiet ventilation brought a significant return toward normal in the carbon-dioxide system (Tables 1 and 2).

Further studies of the electrolyte changes are shown in Table 2. These determinations were made on anaerobically drawn samples of arterial blood, the first being taken during hyperventilation and the second after a 30-minute period of more normal respiration. In both situations the decrease in plasma bicarbonate was more than compensated by a rise in plasma chloride. The increase in ionized protein amounted to less than 1 mEq. per liter. Acid-base equilibrium was therefore accomplished by movement of chloride. The relative changes in plasma bicarbonate and carbon-dioxide tension were as would be expected from the normal carbon-dioxide dissociation curve. Whole-blood buffer base remained normal. Although the patient had been hyperventilating for several months, the fixed base showed only an insignificant decrease, which was shared by sodium and calcium.[13] Thus, no metabolic acidosis (decrease in fixed base or increase in fixed acid) shared in the compensation, and renal regulation was not important. It may be that the periods of relatively normal breathing which occurred when this patient slept limited these more extensive electrolyte changes. Talbott and associates [10] also found shifts between HCO^-_3 and Cl^- to be by far the most important abnormalities in the electrolyte pattern of their patient.

The slight cyanosis of the lips was not due to deficient oxygenation of the arterial blood (saturation, 95 and 98%). The most probable explanation is local dilatation of the small vessels to produce pooling of venous blood— "stagnant anoxia."

We have no certain explanation of the prolonged circulation time. Because there was no change after digitalization, administration of mercurials, and a low-salt diet, left ventricular failure can probably be excluded as a possible cause. Recent investigations [14] have shown that elevated alveolar carbon-dioxide levels produce a constriction of the pulmonary vessels. The converse, pulmonary vasodilatation, in response to lowered alveolar carbon-dioxide pressure, producing a larger volume of blood in the lungs, has not been experimentally attempted. However, if an increased volume of pulmonary blood were present in this patient, we should have an explanation for the delay in passage of test substances through the pulmonary circuit.

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SUMMARY

Physiologic studies on a patient during chronic hyperventilation of psychogenic origin showed lowered plasma carbon-dioxide pressure (pCO_2) and plasma bicarbonate and elevated pH, due to uncomplicated respiratory alkalosis.

In spite of the chronic nature of the overbreathing, compensatory electrolyte shifts involved only the chlorides. This acid-base balance was similar to the changes seen in the usual shorter hyperventilation syndrome and in experimental overbreathing.

Evidence that the fundamental alteration in chronic hyperventilation is a lowered alveolar carbon-dioxide pressure was given by the reversion toward normal of all shifts after even short periods of quiet breathing.

Though the patient refused to consider any psychogenic basis for his symptoms and rejected psychotherapy, he recovered completely within two weeks after discharge from the hospital. During his hospitalization, considerable attention was drawn to his respiration, and he was instructed in measures to forestall the hyperventilation.

Dr. Edward Massie gave us the opportunity to study this interesting patient.

EVALUATION OF THE ELECTROMYOGRAM OF PATIENTS WITH MYASTHENIA GRAVIS

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HARVEY AND MASLAND[1] (1941) introduced a new technique of clinical electromyography which consisted of stimulating accessible motor nerves percutaneously with supramaximal shocks at any desired frequency and recording the action potentials of the associated muscles. Shortly thereafter Harvey and co-workers, using this method, described a characteristic electromyogram of patients with myasthenia gravis.[2] More recently, other investigators[3] have employed this test in an evaluation of new therapeutic agents and procedures in the treatment of myasthenia gravis.

In the past several years, we have studied 21 patients with myasthenia gravis, using the technique of Harvey and Masland. In this report we summarize our impressions of the value of this procedure as a diagnostic test and as an objective indication of the severity of the myasthenic process.

METHODS AND APPARATUS

We used the methods of Harvey and Masland[1] and of Hodes, Larrabee, and German[4] with these modifications: We employed a Grass stimulator, which permitted variation of intensity, duration, frequency, and polarity of galvanic current. The optimal intensity and duration of the stimulus varied from patient to patient but, once determined, was kept constant for any one patient. The nerves stimulated in our study were the ulnar (21 patients) and the facial (4 patients). Action

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potentials were recorded from the abductor digiti quinti (21 patients), the adductor pollicis brevis (2 patients), and the orbicularis oculi (4 patients); cutaneous electrodes were used. Amplification of the action potentials was obtained by means of a three-stage condenser-coupled differential amplifier (modified Grass electroencephalograph). The output leads were connected in parallel circuit to a cathode-ray oscilloscope for visual control, and to a mirror galvanometer, the deflections of which were photographed on bromide paper, a camera with a speed range of 5 cm. to 1 meter per second being used. The amplification varied from patient to patient but was constant for any one series of tests.

Subjects.—We studied 12 normal subjects as controls (9 men and 3 women, their ages ranging from 25 to 42) and 21 patients with myasthenia gravis. The clinical diagnosis of myasthenia gravis was made when (1) the patient had a history and physical findings characteristic of myasthenia gravis and (2) the clinical manifestations subsided unquestionably after the subcutaneous injection of neostigmine methylsulfate,[5] but not after the injection of saline

TABLE 1.—*Summary of Clinical Aspects of Twenty-One Patients with Myasthenia Gravis*

Patient No.	Age, Yr.	Sex	Weakness of Extremity	Dysphagia and/or Dysarthria	Weakness of Facial Muscles	Ptosis and/or Diplopia	Clinical Response to Neostigmine	Electromyogram*		
								Abductor Digiti Quinti		Orbicularis Oculi
								3/Sec.	25/Sec.	
1†	23	F	+	+	+	+	+	+	+	..
2†	30	F	+	+	+	+	+	+	+	..
3†	21	F	+	+	+	+	+	+	+	..
4†	40	F	+	−	+	+	+	+	−	..
5†	54	M	−	−	−	+	+	−	+	..
6†	28	F	+	+	+	+	+	−	−	..
7	5	F	−	−	+	+	+	−	+	..
8	21	F	+	+	+	+	+	+	+	..
9	44	F	+	+	+	+	+	+	+	..
10†	25	F	+	+	+	+	+	+	+	..
11	57	M	+	+	+	+	+	+	−	..
12	44	F	+	+	+	+	+	+	−	..
13†	37	F	+	+	+	+	+	+	+	..
14	3	F	−	−	+	+	+	−	−	..
15†	72	M	+	+	+	+	+	+	−	..
16†	17	F	+	+	+	+	+	−	+	..
17†	32	M	+	+	+	+	+	+	−	..
18	48	M	+	−	+	+	+	+	+	+
19	18	F	+	+	+	+	+	−	−	+
20	>60	F	−	−	+	+	+	−	−	+
21	31	F	−	+	+	+	+	−	−	+

* Electromyograms characteristic of neuromuscular block are indicated by plus signs; normal electromyograms, by minus signs. An electromyogram is considered to be characteristic of neuromuscular block if the 5:1 ratio is less than the normal mean minus twice the standard deviation for normal subjects, i. e., less than 0.95 at a stimulation frequency of 3 per second and less than 0.84 at a stimulation frequency of 25 per second.

† At the time the electromyograms were taken the patient was receiving neostigmine therapy but had had no drug for at least three hours prior to the test. All other patients had never received neostigmine before the time of the test.

solution. For two patients (6 and 14) the diagnosis was confirmed further by the finding that marked intensification of the clinical manifestations developed from the injection of one-twentieth the dose of tubocurarine chloride U. S. P. required to produce muscular relaxation in normal persons. The clinical data on the patients are summarized in Table 1.

Procedure.—The subject was either lying down or seated comfortably in an electrically shielded room. The recording electrodes were applied, and the part was splinted as thoroughly as possible. The stimulating electrodes were applied at the optimal position; threshold and maximal intensities were determined by observing the muscle action potential on the screen of the cathode-ray oscilloscope. The nerve was stimulated at frequencies of 3, 10, and 25 per second

5. The neostigmine (prostigmin®) used in this study was supplied by Dr. E. L. Sevringhaus, of Hoffmann-LaRoche, Inc.

for from 10 to 25 stimuli, with a two-minute rest period after each volley. For some patients electromyographic records were repeated 30 to 45 minutes after subcutaneous administration of 1.5 mg. of neostigmine methylsulfate with 0.6 mg. of atropine sulfate; the position of the electrodes was not altered during this period.

The time required for preparing the patient and for taking and developing the control records was about one hour. Another hour was required when additional records were made after the administration of neostigmine.

Measurement of Records.—We measured only the amplitude of the negative phase of the action potential because previous studies had shown that the negative phase reflects the activity of the muscle fibers directly under the active electrode, whereas the positive phase of the summated potential is a composite of the negative variation in potential near or under the indifferent electrode, the activity of muscle fibers not directly under either electrode, and a positive variation in potential under the active electrode.[3] Measurement of the amplitude of the negative phase was subject to a reading error of 0.5 mm.; the error varied from 1.2 to 3.0%, depending on the amplitude recorded. We have chosen to report the ratio $\frac{\text{amplitude of potential 5}}{\text{amplitude of potential 1}}$, hereafter called

TABLE 2.—*Amplitude of Initial Potential (Abductive Digiti Quinti) and the 5: 1 Ratio in Normal Subjects and in Patients with Myasthenia Gravis*

	Amplitude of Initial Potential, Mv.		5:1 Ratio					
			3/Sec.		10/Sec.		25/Sec.	
	Normal Subject	Myasthenia Gravis	Normal	Myasthenia Gravis	Normal	Myasthenia Gravis	Normal	Myasthenia Gravis
Mean	7.7	8.5	1.01	0.82	1.01	0.87	1.08	0.85
S. D.	1.7	3.3	0.03	0.22	0.08	0.17	0.12	0.21
S. E.	0.4	0.7	0.01	0.04	0.02	0.05	0.03	0.04
No. subjects	12	15*	12	21	12	14	12	21
No. observations	17	26	18	34	18	14	17	34

* In six cases the amplification system was not calibrated for absolute amplitude; valid 5:1 ratios could still be calculated, since the amplification remained the same during any one study.

the 5 : 1 ratio, because a decline in amplitude of successive potentials, usually reaching minimal values by the fifth potential, is the most characteristic feature of electromyograms of patients with myasthenia gravis.

RESULTS

A. *Normal Subjects.*—Amplitude of Initial Potential: For 12 normal subjects, the mean amplitude of the negative action potential obtained from the abductor digiti quinti was 7.7 mv., with a standard deviation of ±1.7 mv. (Table 2). The agreement between these figures and those of Harvey and Masland[1] (6.0 to 9.9 mv.) and of Hodes and associates[4] (6.0 to 16 mv., average 11.3 mv.) is good, considering the many physical and physiologic variables in recording action potentials of muscles by means of electrodes attached to the skin.

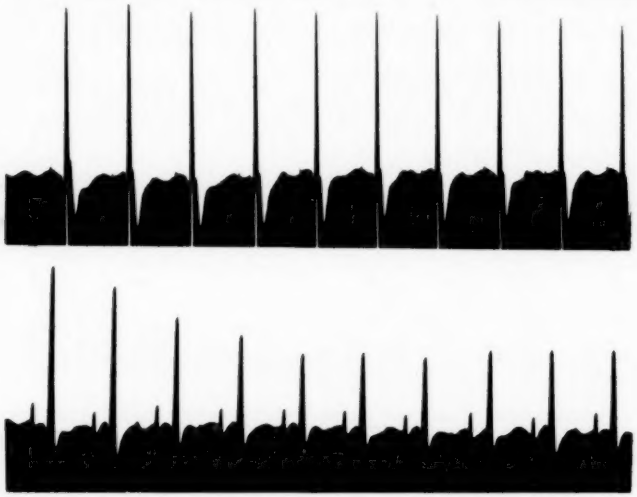
Amplitude of Successive Action Potentials: Our data (Table 2) obtained on normal subjects confirm previous observations that there is no decline in the amplitudes of the 2d to the 10th potentials as compared with that of the 1st, when the nerve is stimulated at a frequency of 3 to 25 times per second.[1] The ratio of the amplitude of the fifth potential to that of the first was 1.01 when the frequency was 3 per second, 1.01 when 10 per second, and 1.08 when 25 per second. A typical record is shown in the Figure.

B. Patients with Normal Records.—An electromyogram of the normal type, described above, does not necessarily mean that the patient is normal. We have

studied a large number of patients complaining of weakness due to well-authenticated disease whose electromyogram obtained by this technique appeared to be completely normal. This number included patients with disease of the central nervous system or with endocrinologic disorders.

It must be emphasized that the electromyographic technique used in this study tests conduction along the peripheral motor nerve, transmission across the neuromuscular junction, and conduction along skeletal muscle fibers. Therefore records will be normal unless there is specific involvement of one or more of these peripheral elements.

C. Patients with Myasthenia Gravis.—We have confirmed the results obtained by other investigators [1] who used this technique in studying patients with myasthenia gravis: 1. The voltage of the initial potential is often normal. The mean voltage



Above, electromyogram from adductor pollicis brevis of a normal subject. Calibration: 0.40 mv.=1 mm.

Below, electromyogram from adductor pollicis brevis of a patient with myasthenia gravis. Calibration: 0.32 mv.=1 mm.

In both records frequency of stimulation was 25 per second, and the small upward negative deflection preceding each large negative spike is a stimulus artifact.

of the initial potential in a group of 15 patients was 8.5 mv., a value which did not differ significantly from the normal (Table 2). The standard deviation for patients with myasthenia gravis was considerably greater than that for the normal group. However, the very low and the very high values bore no consistent relation to the severity or the mildness of the disease, as judged on the basis of clinical manifestations and the 5:1 ratio. Consequently, measurement of the amplitude of the initial potential is of little diagnostic value in this disease. 2. During repetitive stimulation of the motor nerve, the amplitude of the muscle potentials declined progressively, reaching minimal values at the fifth potential for 17 of the 19 patients with records characteristic of neuromuscular block. The mean 5:1 ratio for 21 patients with

TABLE 3.—*5:1 Ratios for Patients with Myasthenia Gravis at Various Frequencies of Stimulation of Abductor Digiti Quinti*

Patient No.	3/Sec.	10/Sec.	25/Sec.
1	0.60	0.60	0.58
	0.95	....	1.06
	0.90	....	1.04
2	0.48	0.58	0.68
3	0.20	....	0.43
4	0.73	0.95	1.00
	0.94	....	1.06
5	1.00	1.08	0.62
6	0.95	1.00	1.00
	1.00	....	1.00
	1.00	....	0.91
	0.96	....	1.00
7	0.95	0.90	0.35
8	0.75	0.62	0.75
	0.73	....	0.69
9	0.63	0.89	0.81
10	0.42	....	0.33
11	0.50	....	0.87
	0.67	....	1.00
12	0.94	....	0.90
	0.98	....	0.94
	1.00	....	1.07
13	0.55	0.73	0.67
	0.44	....	0.56
14	1.00	0.97	0.98
15	0.72	....	1.00
	1.00	....	1.07
16	1.00	....	0.77
	1.00	....	1.00
17	0.85	....	0.87
18	0.86	0.80	0.80
19	0.95	1.03	0.93
20	1.11	1.00	1.10
21	1.00	1.06	1.00

TABLE 4.—*5:1 Ratio and Amplitude of Initial Potential Before and After Subcutaneous Administration of Neostigmine* *

Patient No.	5:1 Ratio			Initial Potential Amplitude, Mv.		
	Before	After	Difference	Before	After	Difference
1	0.60	0.63	+ 0.03	6.7	6.4	— 0.3
4	0.73	0.79	+ 0.06	...	...	.....
8	0.75	0.98	+ 0.23	10.0	10.0	0.0
9	0.63	0.86	+ 0.23	...	...	.....
11	0.67	0.95	+ 0.28	...	...	.....
13	0.44	1.00	+ 0.56	2.5	4.7	+ 2.2
16 †	0.53	0.77	+ 0.24	10.0	10.0	0.0
17	0.85	1.00	+ 0.15	...	...	.....
18	0.86	0.90	+ 0.04	9.3	9.3	0.0
Mean			+ 0.20	...	...	+ 1.9
S. D.			± 0.16	...	...	± 2.0
S. E.			± 0.05	...	...	± 1.7
P			< 0.01	...	...	> 0.2

* All patients for whom data are included in this table had 5:1 ratios which were less than the normal mean minus twice the standard deviation for normal subjects at a stimulation frequency of 3 per second on the day the neostigmine was administered. Others with 5:1 ratios greater than 0.92 at a frequency rate of 3 per second were not included.

† All records were taken from the abductor digiti quinti except that for Patient 16, which was taken from the adductor pollicis brevis. Frequency of stimulation was 3 per second.

myasthenia gravis was 0.82 when the frequency of stimulation was 3 per second, 0.87 when it was 10 per second, and 0.85 when it was 25 per second (Tables 2 and 3). These values are statistically different from those obtained for the normal group. 3. These ratios increased to or toward 1.0 within 30 to 45 minutes after subcutaneous administration of neostigmine methylsulfate (Table 4). A typical record is shown in the Figure.

COMMENT

Value of the Electromyogram in Diagnosis.—Significance of the Myasthenic Type of Electromyogram: An electromyogram with the characteristics described above is believed to be due to neuromuscular block. One reason for this belief is that small doses of curare produce this type of electromyogram at a time when nerve conduction is normal and the muscle still contracts promptly after direct electrical stimulation. Another is that an abnormality in the electromyogram must be due either to alteration in conduction along the individual nerve or muscle fibers or to interference in transmission across the neuromuscular junction. If it were caused by abnormalities in conduction along nerve or muscle, the duration of the summated action potential should be increased because of temporal dispersion. Harvey and colleagues, studying patients with myasthenia gravis, found that after repetitive stimulation of the motor nerve the duration of the summated action potential was decreased concurrently with the decrease in amplitude, and they concluded that the abnormal electromyogram must represent a block at the neuromuscular junction.[2] The block must be incomplete and of such a nature that only a variable portion of the muscle fibers are activated on repetitive stimulation. However, propagation of the impulse along the activated muscle fibers appears to be normal.

A response of the type shown in the Figure is not specific for myasthenia gravis, since it is found also in neuromuscular block produced by drugs such as curare and in the residual paralyses of anterior poliomyelitis.[6] However, these conditions rarely present a problem in differentiation from myasthenia gravis.

In two cases electromyographic evidence of neuromuscular block was present in records from the hypothenar muscles at times when there was no clinical evidence of weakness of the extremities. Since both the patients had weakness of facial and ocular muscles which responded to neostigmine therapy, it appears that in these cases electrical changes preceded clinical evidence of myasthenia in the extremities.

In other diseases, the electromyogram may show abnormalities that are differentiated readily from the typical picture of neuromuscular block. Peripheral nerve injuries and the peripheral neuritides are associated with changes in the duration and form of the potential.[4] Myotonia is associated with a decrement in amplitude, which becomes maximal later in the course of the repetitive stimulation.[7] Botulism is characterized by facilitation (an increase in amplitude of successive action poten-

6. Harvey and Masland.[3] Comroe, J. H., Jr.; Dripps, R. D.; Botelho, S. Y., and Metz, H. T.: The Curare-Like Action of Ether upon Neuromuscular Transmission, Federation Proc. **6**:318, 1947. Grob and Harvey.[3a] Hodes, R.: Electromyographic Study of Defects of Neuromuscular Transmission in Human Poliomyelitis, Arch. Neurol. & Psychiat. **60**:457-473 (Nov.) 1948.

7. Lambert, E. H., and Beckett, S.: Effect of Epinephrine and Other Drugs on Myotonia Congenita, Am. J. Physiol. **163**:728 (Dec.) 1950.

tials on repetitive stimulation).[8] Facilitation has been reported to occur in myasthenia gravis when the frequency of stimulation is high.[2b] We were unable to demonstrate typical facilitation in any of our patients during stimulation at frequencies of 3 to 25 per second, though after the initial abrupt depression the amplitude of the potentials often rose toward initial values.

Significance of Normal Electromyogram in Patients Suspected of Having Myasthenia Gravis: 1. Muscle Tested: The order of involvement of muscles in patients with myasthenia gravis is similar to that in progressive curarization, i. e., the extraocular, facial, and pharyngeal muscles are affected before those of the extremities. It is well known clinically that myasthenia gravis may affect only the extraocular and facial muscles and that the process may involve other muscles much later or never. In our series of patients, ptosis or diplopia was present in 100%, weakness of facial muscles in 95%, weakness of the extremities in 76%, and dysphagia and dysarthria in 71%.

For five of our patients (24%) the electromyograms recorded from the hypothenar muscles were normal regardless of the frequency of stimulation, even though two of the five complained of weakness in the extremity at the time of the test (Table 1). All five had weakness of the ocular and facial muscles. In three of these the orbicularis oculi muscle was tested electromyographically, and each had a record characteristic of neuromuscular block[9]; the technique was not available at the time of study of the other two. We have not studied patients with clinical myasthenia gravis whose electromyograms from the orbicularis oculi muscle were normal. It is possible, were techniques available, that in some patients normal summated electromyograms might be found for all muscles except the extraocular or the pharyngeal. As another example, for Patient 16 the electromyogram from the abductor digiti quinti stimulated at a frequency of 3 per second had a normal 5:1 ratio (1.00) whereas the ratio for the record from the adductor pollicis brevis taken at almost the same time was 0.53. It appears certain that myasthenia gravis would be overlooked in some cases if the only diagnostic test were the electromyogram recorded from the hypothenar muscles.

2. Frequency of Stimulation Employed: It has been reported that the 10th potential of a train of impulses is reduced to a greater extent when the frequency of stimulation is high; i. e., the 10:1 ratio is less at faster rates of stimulation than at slower rates.[2a] Therefore, one might expect that the electromyogram would show evidence of neuromuscular block more consistently when faster rates of stimulation were used. In our series, three patients showed abnormal electromyograms from the abductor digiti quinti when the nerve was stimulated at 25 per second but not at 3 per second; five had abnormal records only at a rate of 3 per second and not at 25 per second, and eight had abnormal records both at slow and at fast rates of stimulation. Clearly, summated electromyogram should be recorded at both low and high frequencies of stimulation to increase the reliability of the procedure.

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8. Masland, R. L., and Gammon, G. D.: Effect of Botulinus Toxin on the Electromyogram, J. Pharm. & Exper. Therap. **97**:499-506 (Dec.) 1949.

9. Botelho, S. Y.; Deaterly, C. F., and Comroe, J. H., Jr.: The Electromyogram from the Orbicularis Oculi Muscle in Normal Human Subjects and in Patients with Myasthenia Gravis, to be published.

3. Relation to Therapy: The summated electromyogram may become indistinguishable from normal records after the administration of an effective dose of neostigmine. This depends, among other factors, upon the severity of the disease. The 5:1 ratio returned to the normal range in four of nine patients so tested (Table 4). It is obvious that the electromyogram is of more diagnostic significance when obtained after neostigmine therapy has been withheld for 4 or more hours, and, again, when recorded 30 to 40 minutes after subcutaneous administration of neostigmine. It should be noted that the amplitude of the initial potential was altered by neostigmine less consistently than the 5 : 1 ratio; this might be anticipated from our inability to demonstrate any correlation between the amplitude of the initial potential and the severity of the disease.

4. Relation to Natural Variations in the Disease: Patients with myasthenia gravis may have spontaneous variations both in their clinical manifestations and in the electromyographic tracings not related to the time of the last administration

TABLE 5.—*Comparison of Electromyograms on Two Different Days*

	Subjectively Weak			Subjectively Strong			Differences	
Patient No.	Time After Neostigmine, Hr.	5:1 Ratio at 3/Sec.	Initial Potential Amplitude (Mv.) at 3/Sec.	Time After Neostigmine, Hr.	5:1 Ratio at 3/Sec.	Initial Potential Amplitude (Mv.) at 3/Sec.	5:1 Ratio at 3/Sec.	Initial Potential Amplitude (Mv.) at 3/Sec.
1	3.5	0.60	6.7	2.0	0.95	12.0	+ 0.35	+ 5.3
4	3.0	0.73	...	3.0	0.94	....	+ 0.21	.....
8	No drug	0.73	10.0	No drug	0.75	10.0	+ 0.02	0
13	2.0	0.44	2.5	48.0	0.55	5.5	+ 0.11	+ 3.0
15	48.0	0.72	4.7	4.0	1.00	5.0	+ 0.28	— 0.3
16 *	3.0	0.53	10.0	7.0	0.90	6.8	+ 0.37	— 3.2
17 *	3.0	0.86	13.1	18.0	1.00	10.7	+ 0.14	— 2.4
						Mean.....	+ 0.20	+ 3.0
						S. D.....	± 0.12	± 4.2
						S. E.....	± 0.04	± 1.7
						P.....	< 0.01	> 0.1

* All records taken from abductor digiti quinti except those for Patients 16 and 17, whose records were taken from adductor pollicis brevis.

of neostigmine. Table 5 shows a mean increase of 0.20 in the 5:1 ratio at times of spontaneous improvement in seven patients with myasthenia gravis. At these times, four of the seven had 5:1 ratios within the normal range, whereas on another day the 5:1 ratios ranged from 0.44 to 0.86 and were clearly diagnostic of myasthenia gravis in each case. There is therefore considerably greater chance for successful electromyographic diagnosis if the procedure is carried out at a time when the patient considers himself to be weak. Again, the 5 : 1 ratio is a more sensitive index than is the amplitude of the initial potential, since change in the latter from day to day was not significant (Table 5).

Summary: The electromyogram was diagnostic of myasthenia gravis for all but two patients (6 and 14). It is likely that the procedure would have been diagnostic for 100% of our patients with myasthenia gravis if action potentials could have been recorded from the orbicularis oculi as well as from the abductor digiti quinti in these two patients. Thus, the electromyographic diagnosis of myasthenia gravis can probably be made consistently if (*a*) several muscle groups are tested, (*b*) several frequencies of stimulation are employed, and (*c*) the test

is performed when the patient has not had therapy for at least three to four hours and at a time when he feels weak. However, the electromyographic technique is not simple. It requires expensive equipment and the services of a well-trained technician. A single test requires at least an hour. The results are reliable only if one is familiar with the technical difficulties which may be encountered, such as those related to the size, type, position, and fixation of recording and stimulating electrodes; the fixation or splinting of the parts involved, and the presence of extraneous potentials that may result from the stimulus current, spontaneous movement, and voluntary movement.

On the other hand, the neostigmine test is far simpler and requires no elaborate apparatus or physiologically trained personnel. Since, in our series, the diagnosis was made correctly for each of the 21 patients by the response of the patient to neostigmine as opposed to placebos, the neostigmine test is obviously preferable to electromyography as a routine diagnostic procedure.

TABLE 6.—*Comparison of 5: 1 Ratio and Daily Maintenance Dose of Neostigmine* *

Patient No.	Dose, Mg./Kg.	5:1 Ratio †	Initial Potential Amplitude, Mv.
13	2.31	0.44	2.5
10	2.20	0.33	...
2	1.55	0.48	...
5	1.51	0.62	18.5
21	1.41	0.80 ‡	7.0
19	1.06	0.52 ‡	12.3
16	1.06	0.53 §	4.3
4	0.93	0.73	...
9	0.92	0.63	...
18	0.89	0.59 ‡	9.3
12	0.89	0.90	9.0
11	0.58	0.50	...
8	0.58	0.62	10.0
6	0.46	0.96	10.5

* Records were taken from the abductor digiti quinti unless stated otherwise.
† The 5:1 ratios are the lowest obtained at any time at any frequency of stimulation from any muscle tested. The initial potential amplitudes are all from the abductor digiti quinti muscle. Data for dose per kilogram of body weight are not known for seven patients.
‡ The orbicularis oculi was the muscle tested.
§ The adductor pollicis brevis was the muscle tested.

The electromyogram is useful with patients resistant to neostigmine therapy (not encountered in our series), patients whose response to neostigmine is uncertain or is clouded by emotional or hysterical factors, in the objective evaluation of drugs used in the therapy of myasthenia gravis, and in the study of the pathologic physiology of the disease.

Value of the Electromyogram in Estimation of Severity of Myasthenia Gravis.—After the diagnosis of myasthenia gravis had been made, patients were placed on maintenance doses of neostigmine bromide. We have already pointed out that there was no correlation between the amplitude of the initial potential and the severity of the disease in the present study. Table 5 shows that the 5: 1 ratios of the patients with severe myasthenia were lower in general than the 5: 1 ratios of the patients with mild myasthenia. However, the range of the ratios was wide, and there was considerable overlap. Better correlation might be obtained if the

electromyograms were recorded routinely from the muscles affected earliest in the disease (facial and extraocular).

As would be expected from clinical experience, there was no correlation between the 5:1 ratio and the duration of the disease (Table 7).

Until further data are available, one cannot judge the severity of the disease on the basis of the electromyogram alone.

SUMMARY

Action potentials were recorded from different muscle groups during supramaximal stimulation of the motor nerve in normal subjects and in patients with myasthenia gravis (method of Harvey and Masland). The characteristic electromyographic pattern of neuromuscular block was found consistently in patients with myasthenia gravis only when several muscles were tested and various frequencies of stimulation were used. Because the electromyographic technique is laborious, its use in this disease will probably be limited to large medical centers with unusual diagnostic problems, in the further study of the underlying physiological pathology of neuromuscular disorders, and in the objective evaluation of therapeutic measures.

TABLE 7.—*Comparison of 5:1 Ratio and Duration of Diseases**

Patient	Duration of Disease (Mo.) from Onset of Symptoms	5:1 Ratio †	Patient	Duration of Disease (Mo.) from Onset of Symptoms	5:1 Ratio
14	3	0.97	7	36	0.35
15	7	0.72	2	60	0.48
19	8	0.58 ‡	16	72	0.53 §
12	9	0.90	10	84	0.42
11	10	0.50	17	84	0.86
8	12	0.73	6	84	0.95
3	24	0.20	4	84	0.73
20	24	0.75 ‡	18	108	0.59 ‡
			13	192	0.44

* Recording was from the abductor digiti quinti unless stated otherwise.

† The 5:1 ratios in this table are the lowest recorded at any time and from any muscle in each patient. Data as to duration of symptoms were not available for four patients.

‡ Orbicularis oculi was the muscle tested.

§ The adductor pollicis brevis was the muscle tested.

Dr. Martin Larrabee and Dr. Robert Hodes aided in the early studies, and Dr. George Gammon and Dr. Irving Leopold referred many of the patients to us.

HYPOTHALAMIC SYNDROMES COMPLICATING ANTIRABIES VACCINATION

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PRIOR to the introduction of antirabies vaccine by Pasteur in 1885, both furious and paralytic rabies had been described as occurring in man. The latter was apparently rare, and, although described by van Swieten in 1753, its occurrence was not widely known. Shortly after the introduction of the vaccine, fatal cases of paralysis, occurring during or after treatment, were recorded. These were ascribed by Pasteur and his protagonists to the street virus, producing "dumb" rabies; in other words, the vaccine had failed to protect. They insisted that the fixed virus of the vaccine was harmless. Pasteur's antagonists were quick to draw a parallel between the fatal paralysis and the state of rabbits infected with fixed virus and claimed that the fixed virus of the vaccine was responsible. The condition was somewhat caustically termed by Peter, Pasteur's chief antagonist, *rage de laboratoire*. The hypothesis that the fixed virus was innocuous was rendered untenable when persons treated with the vaccine after being bitten by dogs subsequently shown to be nonrabid were proved to have rabies by histological observations at autopsy and by transmission experiments. It must be appreciated, therefore, that during or after treatment with rabies vaccine, paralytic rabies, due either to the street virus or to the fixed virus, may well be encountered. Both these conditions are accepted as fatal.

Some three years after the introduction of the vaccine there were reported cases of a condition considered to be paralytic rabies which was not necessarily fatal. According to Stuart and Krikorian,[1] Gonzales described three such cases in 1888. Laveran,[2] in 1891, described a case of transient paralysis of the legs commencing eight days after the start of treatment. Within a short time a number of cases were reported, and it would appear that the authors considered that the condition was due to modification of the street virus. This hypothesis was no longer tenable when paralysis occurred in persons bitten by healthy dogs. For example, Tonni[3] reported such a case and concluded that the causal factor was present in the vaccine.

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1. Stuart, G., and Krikorian, K. S.: The Neuro-Paralytic Accidents of Anti-Rabies Treatment, Ann. Trop. Med. **22**:327, 1928.

2. Laveran, A.: D'une forme atténuée de la rage observée pendant le cours du traitement par les inoculations préventives, Bull. et mém. Soc. méd. hôp. Paris **8**: 191, 1891.

3. Tonni, S.: Compte rendu statistique de l'Institut du Caire, 1899-1901, p. 42.

Remlinger,[4] in 1905, collected records of 40 cases occurring among 107,712 persons treated, and Marie, Remlinger, and Vattee,[5] in 1927, reported a total of 529 cases among 1,164,264 persons treated. To this condition the term "paralytic accident of Pasteur treatment" has been given. This designation does not include paralytic rabies due to street virus or fixed virus; it is reserved for paralytic conditions resulting from the action upon the brain, spinal cord, or peripheral nerves of some as yet undetermined substance contained in the vaccine.

The paralytic accidents may be classified as follows:

Group 1 (20%): Simple neuritis involving either the cranial or the peripheral nerves. The seventh nerve is most commonly affected. Other cranial nerves liable to be attacked are the 3d, 6th, 9th, 10th, and 12th.

Group 2 (5%): Dorsolumbar myelitis in which initial fever is slight. It is characterized by weakness; paresthesia, especially of the legs; girdle pain, which may be severe; sphincter disturbances, and termination in paralysis, particularly of the legs. Recovery occurs in most cases within two to three weeks.

Group 3 (30-40%): Paralysis of the Landry type. The onset is sudden, with fever, severe headache, vomiting, insomnia and restlessness, and ascending paralysis. In one-third of the cases bulbar paralysis develops.

Group 4: Gordon's syndrome, which is essentially a meningoencephalomyelitis, with a high mortality.

Group 5: Meningoencephalitis without paralysis. This is a rare condition, and, as far as I am aware, only three cases have been described in the literature.

The purpose of this paper is to present two additional cases of meningoencephalitis without paralysis. An additional, and most unusual, feature of each case was the persistence of evidence of disturbance of hypothalamic function. In one case a syndrome consistent with diencephalic-autonomic epilepsy was a sequela, and in the other, a narcolepsy-obesity syndrome.

REPORT OF CASES

Case 1.—A Chinese schoolboy, aged 11 years, was first seen in consultation on March, 1, 1950. He had been bitten on the forearm by a dog on Feb. 18. The dog was not detained. On the day of the bite a course of daily injections of 2.5 cc. of Semple vaccine was commenced. No reaction was experienced until after the eighth injection, given on the morning of Feb. 26. In the afternoon the child was listless and disinclined to play, and in the evening he complained of severe headache followed rapidly by nausea, retching, and vomiting. The mother was insistent that the child had at this stage a "high fever." In the early hours of Feb. 27 he had a series of generalized myoclonic convulsions and subsequently lapsed into a semicomatose state, with incontinence. With difficulty, he could be roused sufficiently to take fluids, but showed no interest in his surroundings or his attendants.

Examination (March 1).—The patient, a well-nourished and well-developed boy, showed evidence of dehydration. The skin was flushed, and sweating was profuse. It had been noted by the nurses that the sweating showed periods of exacerbation, during which sweat literally streamed from him. This was especially noticeable on the face. In the 12 hours after his admission to the hospital the temperature ranged from 99.2 to 101 F. and the pulse rate from 94 to 102 per minute. The respiration rate was 32 per minute; breathing was very irregular and of Biot's type. The blood pressure was 110/60.

4. Remlinger, P.: Accidents paralytiques au cours du traitement antirabique, Ann. Inst. Pasteur **19**:625, 1905.

5. Marie, A. C.; Remlinger, P., and Vattee, H.: Report to the International Rabies Conference Organized by the League of Nations, 1927.

The child was stuporous and had been so since admission. He could be roused sufficiently to drink, when he consumed copious quantities of fluids. Frequently, however, he would punctuate his drinking by forcibly spitting out the fluid. During the course of the examination it was noted that there were phases of noisy chewing with lip smacking punctuated by sucking with the mouth half-open. The picture was reminiscent of the Chinese habit in eating from a bowl. According to the mother, this had been present for some days. She assumed that he was hungry, but on each occasion that she had forced solid food into his mouth it was invariably spat out and the chewing ceased.

There was pronounced nuchal rigidity but no Kernig sign. The pupils were equal and widely dilated and reacted partially and sluggishly to light. Hippus was present. Except for depression of the abdominal skin reflexes, the rest of the neurological findings were normal.

Examination of the remaining systems showed no abnormality.

Spinal Fluid: Lumbar puncture disclosed a cerebrospinal fluid pressure of 190 mm. The cell count was 120 per cubic millimeter, and of these 90% were lymphocytes and 10% polymorphonuclear leucocytes. The protein was 100 mg. per 100 cc. The sugar and chloride level were normal. The Wassermann reaction was negative, and culture of the fluid was sterile.

Peripheral Blood: The hemoglobin content was 12.2 gm. per 100 cc.; the red blood cell count was 4,200,000, and the white blood cell count, 17,000 per cubic millimeter, with a differential count of 80% neutrophiles, 2% eosinophiles, 16% lymphocytes, and 2% monocytes.

Urine: The 12-hour volume was 210 cc., with a specific gravity of 1.020. The sodium chloride content was less than 1 gm. per liter. Steps were taken to establish water and salt balance.

Sensitivity to Vaccine: In order to determine whether sensitivity to the vaccine existed, 0.1 cc. of a 1:100 dilution of the vaccine was injected intradermally. Although the early reaction was, in my opinion, abnormally severe, the fully developed reaction could not be read, for the parents decided to remove the patient from the hospital for traditional Chinese medical treatment.

Subsequent Course of Illness.—He was next seen on April 28, 1950, on his admission to the Department of Medicine, University of Hong Kong, Queen Mary Hospital, from the outpatient practice.

A detailed history of the intervening period could not be obtained, for the mother had returned to her native village in China. It would appear that after he left the hospital his condition remained unchanged for a few days and thereafter there was progressive return to consciousness. The child's behavior had changed. For the greater part, he would remain quietly in a corner of the house playing with his toys, paying little heed to others in the room. He refused to associate with other children. At times, he became restless and difficult to control, and any interference provoked an outburst of violent temper. These periods were frequently, but not invariably, followed by attacks of extreme irritability, restlessness, and profuse sweating. Such attacks varied widely in severity and duration, and the father was unable to state their frequency. They were invariably followed by periods of deep sleep. No circumstances were known to precipitate the attacks.

His appetite was remarkable. On occasions he would eat enormous quantities of rice, more than twice his father's maximum amount, and the food would be devoured in ravenous fashion. Even after such a meal he had been found eating uncooked vegetables and raw pork, but at no time did he consume other than foodstuffs. These paroxysms of voracious appetite, according to the father, followed the attacks of severe irritability. They were commonly preceded by complaint of hunger and abdominal pain. Frequency of micturition was also a common concomitant. The periods of abnormal appetite alternated with days during which solid food was refused and he was content to drink copious amounts of fluid.

Examination revealed severe emaciation. The skin was flushed, and sweating was pronounced. He was restless and appeared unduly apprehensive. The temperature was 98.2 F.; the pulse rate, 84 per minute, and the respiration rate, 20 per minute. The blood pressure was 100/70.

Systematic examination revealed no abnormality. Owing to language difficulties, it was impossible to assess the child's mental state.

Findings on Second Investigation.—Urine: The 24-hour volume averaged 1.3 liters, and the sodium chloride content was within normal limits. No abnormal constituents were present.

Peripheral Blood: The hemoglobin measured 13.2 gm. per 100 cc. The red blood cell count was 4,600,000 per cubic millimeter. The white blood cell and differential counts were within normal limits.

Lumbar Puncture: The findings were normal.

Roentgenogram of Skull: No abnormality was detected.

Sensitivity Test: In order that it might be determined whether sensitivity to the vaccine had persisted, 0.1 cc. of a 1:100 dilution of the vaccine was injected intradermally. The response was not abnormal.

Progress in Hospital.—On the evening of the day of his admission, the restlessness increased, and the child became greatly agitated and apprehensive. He was aware that a fit was impending. With difficulty he was constrained to remain in bed. Any attempt to restrain his movements,

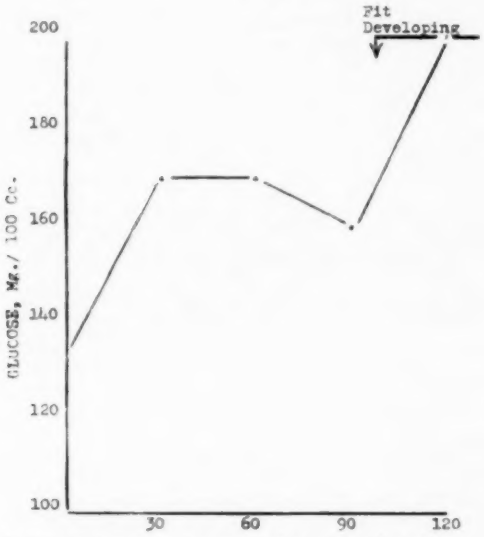

Fig. 1 (Case 1).—Glucose tolerance curve, the test terminated by onset of a fit.

which throughout were purposeful, increased the agitation and restlessness and were violently resisted. This phase was followed by extreme flushing of the skin and profuse sweating. The flushing was generalized and symmetrical, but was especially pronounced over the ears, face, hands, and feet. Sweat literally streamed from him. It was most profuse over the face, neck hands, and feet. The bedding rapidly became sodden. The pupils were widely dilated and the eyes staring, with wide retraction of the lids and absence of blinking. The pulse rate increased to 130 per minute, and the blood pressure climbed to 150/90. The respiration rate fell to 7 per minute, and breathing was irregular in time and depth. Examination of the chest revealed diffuse coarse rales. Cough was frequent, but any sputum produced was swallowed. Salivation was marked and was associated with frequent noisy swallowing. Lacrimation was severe. The picture was an unpleasant one.

The flushing and the sweating gradually diminished, and the patient fell into a deep sleep, from which he could be roused with difficulty, an interference which was resented.

During sleep the child appeared dehydrated, evidence of the loss of salt and water resulting from the remarkable sweating.

Three attacks, similar in character and varying in duration and severity, were witnessed during his stay in the hospital.

A glucose tolerance test was carried out. This was terminated by a fit during which a specimen of blood was obtained. The results are shown in Figure 1. It will be seen that the fasting level was unduly high and that after onset of the fit there was a sharp elevation of the blood sugar level.

Throughout his stay in the hospital the patient refused solid food and at no time showed evidence of the voracious appetite described by his father. Regrettably, further investigation was prevented by the father's demanding his discharge from the hospital four days after his admission.

The child was apparently taken back to the family village in China, and all efforts to trace him have proved useless.

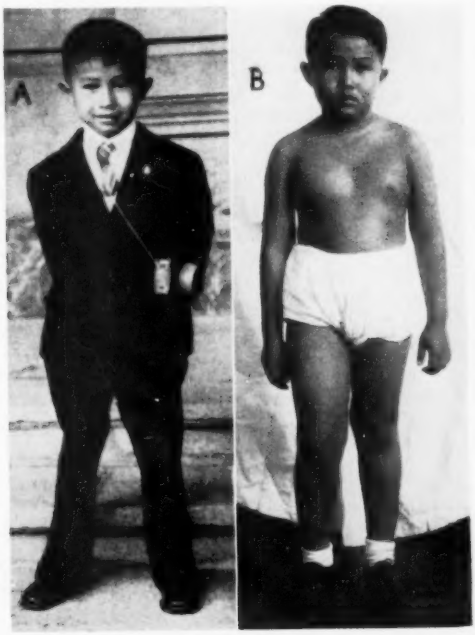

Fig. 2 (Case 2).—*A*, photograph of patient taken three months before onset of encephalitis (weight, 49 lb. [22.2 kg.]); *B*, photograph taken one year after the encephalitis (weight, 94 lb. [42.6 kg.]).

CASE 2.—A Chinese schoolboy, aged 8½ years, was first seen in consultation on Sept. 15, 1950. On July 22, 1949 he had been bitten on the left leg by a dog proved by survival to be nonrabid. Two days after the bite, daily injections of 2.5 cc. of Semple vaccine were started, and, for no apparent reason, the course was completed. No reaction occurred until the day of the last, i.e. the 14th, injection, when the patient complained of severe headache, stiff neck, and shivering, and the temperature climbed to 104 F. There was no reaction at the site of injection. The symptoms persisted for about three days, when he became apyrexial. The child slept throughout the greater part of the illness, but with resolution of the fever the sleepiness persisted. He could be roused with difficulty; once roused, however, he would reply rationally to questions and take food, but on being left he would fall asleep once more. The experienced general practitioner who attended him stated that there was no evidence of paresis at any time and that the picture in the acute phase was consistent with that of meningoencephalitis.

The picture of hypersomnia was gradually replaced by narcolepsy. In the intervals between attacks the child was normal, but at irregular and frequent intervals he would suddenly fall asleep. He could readily be aroused. These attacks were so frequent as to interfere materially with his schooling.

From the onset of symptoms, in August, 1949, until he was first seen, in September, 1950, there had been rapid and progressive gain in weight. In this period his weight had increased from 49 to 84 lb. (22.2 to 38.1 kg.) (Fig. 2).

On examination, the boy appeared alert and normally intelligent for his age. He was obese, and the fat was distributed in feminine fashion. The arms, forearms, and legs were involved, but the hands escaped. Silvery striae were present over the lower part of the abdomen and buttocks. Systematic examination revealed no other abnormality. During the course of the interview he had two attacks of narcolepsy.

He was admitted to the University Department of Medicine, Queen Mary Hospital, on Sept. 15, for study.

Examination.—The urine was normal. The peripheral blood was within normal limits. A roentgenogram of the skull revealed no abnormality. The findings on lumbar puncture were normal.

A glucose tolerance test showed a decided increase in carbohydrate tolerance.

In order to determine whether sensitivity to the vaccine existed, 0.1 cc. of a 1:100 dilution was injected intradermally. The reaction could not be considered abnormal when compared with normal controls.

The patient was given amphetamine, and the dose was adjusted so as not to interfere with normal sleep.

He has been seen at intervals since his discharge. The narcolepsy is well controlled with amphetamine, but on withdrawal of the drug the attacks return. His weight has remained constant. While he is taking the drug, his appetite is impaired, but on withdrawal his appetite is greatly increased and his weight climbs rapidly.

COMMENT

The incidence of neuroparalytic accidents with the Pasteur treatment is very low. Greenwood [6] placed the incidence at 1:5,814 in a series of 1,290,758 patients treated with the vaccine. Herron [7] stated that the liability to accident after treatment with live-virus vaccine is four times as great as after treatment with killed-virus vaccine. The Semple vaccine is a phenol-killed-virus vaccine, belonging to the second category. The rarity of the condition, however, does not relegate it to a position of purely academic interest.

Although children constitute the majority of patients attending for antirabies vaccination, they are much less prone to paralytic accidents. Thus, in a series of 149 cases cited by Stuart and Krikorian,[1] 135 were of patients above 15 years, and only 14 were of patients below that age. The ages of the patients reported here were 11 and 8½ years.

The type of reaction described in this communication is exceedingly uncommon. As far as we are aware, three cases of meningoencephalitis without paralysis have been described in the literature. Horack,[8] and Pickar and Kramer [9] each

6. Greenwood, M.: Tenth Report on Data of Anti-Rabic Treatments Supplied by Pasteur Institutes, Bull. Health Organ. League of Nations **12**:301, 1945-1946.

7. Herron, P. H.: Fatal Paralysis Following Anti-Rabies Treatment, New Orleans M. & S. J. **93**:450, 1944.

8. Horack, H. M.: Allergy as a Factor in the Development of Reactions to Anti-Rabic Treatment, Am. J. M. Sc. **197**:672, 1939.

9. Pickar, D. N., and Kramer, H. M.: Encephalitis Complicating Vaccination for Rabies, South. M. J. **42**:127, 1949.

described one case with complete recovery, and a fatal case of the same type was reported by the Massachusetts Department of Public Health.[10] Koenigsfeld[11] reported a case in which the main feature was optic neuritis with symptoms suggestive of encephalitis. In this case the other neurological findings were doubtful. In a footnote to Koenigsgeld's paper, the editor mentioned an unpublished case of optic neuritis ascribed to the effects of antirabies vaccination. No mention is made of the other neurological findings.

There is general agreement on the pathology of the condition. In addition to alterations in ganglion cells, varying from simple swelling and early nuclear changes to karyolysis and karyorrhexis, there are perivascular demyelination, variable perivascular cuffing, and microgliosis. Bassoe and Grinker[12] emphasized the occurrence of capillary damage with swelling of the endothelium, including complete obstruction. It is well recognized that the pathology of the paralytic accidents of rabies vaccinations is remarkably similar to that of the encephalomyelitis following vaccinia, smallpox, measles, and chickenpox. Indeed, Grinker and Bassoe,[13] in a suggested classification of nonsuppurative encephalitis, grouped all five conditions with certain cases of disseminated encephalomyelitis as showing focal perivascular, incomplete softenings involving the whole nerve fiber, coalescence of lesions to form softenings, microgliosis, mild lymphocytic reaction, and secondary gliosis. If one assumes the almost exact pathological identity of these conditions, then the occurrence of encephalitis without paralysis is to be anticipated after antirabies vaccination, for such a condition has been recognized after vaccinia and has been reported after smallpox (Marsden and Hurst[14]) and measles (Ford[15]).

Again, from the same considerations, the persistence of syndromes consistent with hypothalamic damage is not surprising, since well-defined clinical conditions arising from damage to the hypothalamic nuclei or their connections, for example, the somnolence-obesity syndromes and diabetes insipidus, have been ascribed to encephalomyelitis other than that following antirabies vaccination.

The cause of the paralytic accidents remains obscure. The theories which have arisen may be classified as of two types: The first postulates a virus origin, and the second incriminates the nerve tissue contained in the vaccine.

The hypothesis that the street virus, modified by the vaccine, is responsible is untenable, provided it is accepted that naturally occurring rabies in animals is invariably fatal. As in Case 2, the biting animal has been proved in many cases to be nonrabid.

Many investigators subscribe to the belief that the accidents are the result of infection with the fixed virus of the vaccine. In this connection, it should be

10. Reactions to Anti-Rabic Vaccine, editorial, New England J. Med. **237**:828, 1947.

11. Koenigsfeld, E. G. H.: Neuroparalytic Accident Following Anti-Rabic Vaccination, J. Roy. Army M. Corps **85**:254, 1945.

12. Bassoe, P., and Grinker, R. R.: Human Rabies and Rabies Vaccine Encephalomyelitis, Arch. Neurol. & Psychiat. **23**:1138 (June) 1930.

13. Grinker, R. R., and Bassoe, P.: Disseminated Encephalomyelitis: Its Relation to Other Infections of the Nervous System, Arch. Neurol. & Psychiat. **25**:723 (April) 1931.

14. Marsden, J. P., and Hurst, E. W.: Acute Perivascular Myelinoclasis in Smallpox, Brain **55**:181, 1932.

15. Ford, F. R.: Nervous Complications of Measles, with Summary of Literature and Publication of 12 Additional Case Reports, Bull. Johns Hopkins Hosp. **43**:140, 1928.

remembered that Kelser,[16] while filtering phenolized vaccine through wire gauze, recovered coarse particles which contained live virus capable of producing fixed-virus rabies in rabbits. "Killed" vaccines in which phenol is employed, such as the Semple vaccine, cannot therefore be assumed to be free of living vaccine.

Remlinger [6] considered that a rabies toxin, together with the fixed virus, was responsible. This view has received little support.

Perhaps the most intriguing of the infective theories is that which postulates activation of a latent virus. Greenfield,[17] in discussing encephalomyelitis following vaccinia and eruptive fevers, stated:

> Both the post-vaccinal and other forms of encephalitis which follow eruptive fever are not directly due to the virus of the preceding fever but to another virus which is either stimulated to activity or is directed against the nervous system by the exanthem.

Protagonists of this view would include the encephalomyelitis of rabies vaccination. This concept has been discussed by Marsden and Hurst,[14] who believe that the encephalomyelitis of vaccinia, eruptive fevers, and antirabies vaccination is an independent exanthem, which they term acute perivascular myelinoclasis. It should be noted that Babonneix and Sigwald [18] expressed the view that fixed virus of the vaccine activated a latent virus in the central nervous system.

The most popularly supported theory is that such an accident is the expression of a sensitization reaction to the nerve substance contained in the vaccine. This view was first advanced by Harvey and McKendrick.[19] That allergic reactions to rabies vaccine occur cannot be denied. Horack [8] classified the extraneural reactions as follows: (1) a generalized rash, appearing soon after commencement of treatment and reacting to epinephrine; delayed reactions of the tuberculin type, occurring at the site of injections; reactions similar to 2, but severer and frequently associated with fever, headache, nausea, and adenopathy.

Horack [8] reported a personal or familial history of allergic disease in 13 of 16 cases, an incidence of 87.5%, as compared with 33% for a group in which no paralytic accidents occurred. Sellars [20] reported a history of previous antirabies vaccination in five of seven cases, and Latimer, Webster, and Gurdjian,[21] such a history in an additional two cases. Experimental observations lend credence to this view. Schwentker and Rivers [22] showed that emulsions of nerve tissue acted as antigens and produced an antibody response in rabbits. Similar results, with production of encephalomyelitis, were reported by Kabat, Wolf, and Bezer [23] and

16. Gordon, J. E., and others: Virus and Rickettsial Diseases with Especial Consideration of Their Public Health Significance, Cambridge, Mass., Harvard University Press, 1940.

17. Greenfield, J. G.: Pathology of Measles Encephalomyelitis, Brain **52**:171, 1929.

18. Babonneix, L., and Sigwald, J.: Paraplégie flasque au cours du traitement antirabique, Ann. méd. **26**:114, 1929.

19. Harvey, H., and McKendrick, A. G.: Theory and Practice of Anti-Rabic Immunization, Scientific Memoirs, n. s. No. 30, Government of India, 1907.

20. Sellars, T. F.: Limitations of Anti-Rabic Treatment, J. M. A. Georgia **35**:132, 1946.

21. Latimer, F. R.; Webster, J. E., and Gurdjian, E. S.: Neurological Complications of Rabies Vaccine, A. M. A. Arch. Neurol. & Psychiat. **65**:16 (Jan.) 1951.

22. Schwentker, F. F., and Rivers, T. M.: Antibody Response of Rabbits to Injections of Emulsions of Homologous Brain, J. Exper. Med. **60**:559, 1934.

23. Kabat, E. A.; Wolf, A., and Bezer, A. A.: Rapid Production of Acute Disseminated Encephalomyelitis in Rhesus Monkeys by Injection of Heterologous and Homologous Brain Tissue with Adjuvants, J. Exper. Med. **85**:117, 1947.

by Morrison.[24] Kirk and Ecker [25] described an increased antibrain-antibody titer in the serum of patients with rabies-vaccine encephalitis. Pickar and Kramer [9] considered that the course in their case of encephalitis was favorably influenced by an antihistamine drug (diphenhydramine [benadryl®]) and concluded that further clinical trial was warranted.

In the cases reported in this communication there was no previous history of rabies vaccination; neither was there a personal or a familial history of allergy. The significance in Case 1 of the positive reaction to the intradermal test in the acute phase of the illness is difficult to assess, for on the patient's second admission to the hospital the reaction was negative. This conversion also renders without significance the negative response in Case 2 one year after the acute incident.

A further theory is that of Stuart and Krikorian,[1] who concluded from observations on experimental animals that the neuroparalytic accidents were not anaphylactic phenomena, but that the cause was presumably a constituent of normal nerve substance, which is toxic and capable of producing paralysis. They considered, however, since they could establish no relation between the dose and the occurrence of paralysis, that there was strong evidence in favor of individual hypersensitiveness to the cytotoxin.

The fits which occurred in Case 1 were consistent with the syndrome of diencephalic-autonomic epilepsy described by Penfield.[26] Penfield's case was one of a tumor of the third ventricle with hydrocephalus. The picture in the present case was characterized by widespread activity of the autonomic nervous system, and, although sympathetic activity predominated, it would appear that the parasympathetic nervous system was also involved.

This picture may well be due to neural discharge from centers in the hypothalamus. For example, Sayers, Shenkin, and Yaskin [27] reported a case of involuntary autonomic discharges, among other manifestations of disturbance of hypothalamic function, due to a granulomatous lesion strictly confined to the hypothalamus.

On the other hand, disturbance of hypothalamic function is known to result from outside the hypothalamus. The phenomenon of "sham" rage in animals is characterized by violent autonomic reactions. This phenomenon has been studied by Bard [28] in decorticate cats. Fulton and Ingraham [29] reported a similar reaction in cats when an incision was made just anterior to the supraoptic nuclei. Temporary autonomic imbalance following prefrontal leucotomy in man has been

24. Morrison, L. R.: Disseminated Encephalomyelitis Experimentally Produced by Use of Homologous Antigen, Arch. Neurol. & Psychiat. **58**:319 (Oct.) 1947.

25. Kirk, R. C., and Ecker, E. E.: Time Appearance of Antibodies to Brain in the Human Receiving Anti-Rabies Vaccine, Proc. Soc. Exper. Biol. & Med. **70**:734, 1949.

26. Penfield, W.: Diencephalic Autonomic Epilepsy, Arch. Neurol. & Psychiat. **22**:358 (Aug.) 1929.

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described by many investigators, among them Reitman.[30] Engel and Aring [31] reported hypothalamic dysfunction in a patient with a long-standing lesion involving the dorsomedial nucleus, internal medullary lamina, and lateral nucleus of the thalamus. It would appear, therefore, that abnormal hypothalamic activity occurs as a release phenomenon from destruction of the cortical representation of the autonomic nervous system or of the direct and indirect pathways connecting this system with the hypothalamus. In this case the functional integrity of the hypothalamus was maintained, and this suggests that the lesion or lesions responsible for the discharges lie outside the hypothalamus.

The attacks of voracious appetite, abdominal pain, and frequency of micturition described by the father as occurring after the fits, regrettably, were not witnessed in the hospital. The picture suggests parasympathetic preponderance. Beattie [32] has shown that gastric hypertonia, hypermotility, and hypersecretion result from stimulation of the tuber cinereum in animals. There is, in addition, increased bladder tone. Consequently, such attacks may well result from neural discharge from parasympathetic centers. However, it may also result as a release phenomenon, for bulimia is a common component of the prefrontal lobotomy syndrome. A third possibility exists. According to Brain and Strauss,[33] vagotonia can probably also result from destructive lesions involving the posterior hypothalamic nuclei, which are held responsible for the phenomenon of "sham" rage. It is possible, therefore, that in the period following a proportion of the fits there was selective depression of the posterior hypothalamic nuclei, which were mainly involved in the fit, with consequent preponderance of parasympathetic activity.

The lesion in Case 2, which had persisted for two years, could be localized definitely in the hypothalamus.

The observation by Fröhlich, in 1901, of obesity and genital hypoplasia associated with a tumor in the region of the pituitary body suggested that hypofunction of that organ was responsible. Bailey and Bremer,[34] among others, recognized the occurrence of obesity following lesions confined to the hypothalamus. Smith [35] confirmed these observations and showed conclusively that extirpation of the pituitary alone did not produce obesity. Hetherington [36] showed that lesions restricted to the hypothalamus could produce obesity whether the pituitary was removed before or after production of the lesions. Brobeck [37] reviewed the experimental production

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of hypothalamic obesity and concluded that in the rat lesions must be bilateral and must be situated in or near the ventromedial nucleus. Camus, Gournay, and LeGrand [38] considered that the paraventricular nucleus was involved. Narcolepsy may be associated with a remarkable number of conditions, but among the well-established relations is that of obesity with or without genital atrophy.

SUMMARY

Two cases of meningoencephalitis without paralysis complicating antirabies vaccination are described. In each case disturbance of hypothalamic function followed the acute incident. In one case a syndrome consistent with diencephalic-autonomic epilepsy occurred, and in the other a narcolepsy-obesity syndrome was present.

The incidence and etiology of the accidents of rabies vaccination are briefly considered.

The neurological considerations are discussed.

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TRIHEXYPHENIDYL (ARTANE®), STRAMONIUM, AND NONCHEMOTHERAPY OF PARALYSIS AGITANS

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SINCE the use of scopolamine by Gnauck [1] in 1882 in cases of paralysis agitans, an unknown number of chemotherapies have been studied.[2] None has been effective in arresting or reversing the course of the disorder. At best, a few have been considered relatively effective in relieving some of the more distressing symptoms in some patients. Walshe [3] stated that no one drug or combination of drugs has established its supremacy over the others.

In 1949 Doshay and Constable [4] reported their experience with the use of trihexyphenidyl (artane®) in a series of 117 patients. They found it to be more effective than atropine or belladonna derivatives in producing what they labeled "favorable results" in patients suffering from paralysis agitans. Their findings were confirmed by Corbin.[5] Other clinical studies [6] have confirmed the conclusion that trihexyphenidyl has merits in the armamentarium of treatment of paralysis agitans. There is some disagreement on its relative effectiveness.

Doshay and Constable did not report their findings in objective measurable criteria. They stated that "if symptoms were lessened to any appreciable degree

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1. Gnauck, R.: Über die Anwendung des Hyoscin bei Geisteskranken, Charité-Ann. **7**:448-465, 1882.

2. Gowers (A Manual of Diseases of the Nervous System, Ed. 2, Philadelphia, The Blakiston Company, 1893, Vol. 2) credited Charcot with suggesting hyoscyamine, later replaced by scopolamine.

3. Walshe, F. M. R.: Diseases of the Nervous System, Ed. 6, Baltimore, Williams & Wilkins Company, 1949.

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6. Canelis, M.; Farnell, F. J., and McGavack, T. H.: Clinical Experiences in Parkinsonism with a New Type of Anti-Spasmodic (Artane), Am. J. M. Sc. **218**:655-659, 1949. Harris, T. H., and Torrens, J. K.: The Use of Artane in Parkinsonism, Digest Neurol. & Psychiat. **18**:135-136, 1950. Salzer, H. M.: Artane in Treatment of Parkinsonism, Dis. Nerv. System **11**:77-78, 1950. Schwab, R. S., and Tillmann, W. R.: Artane in the Treatment of Parkinson's Disease, New England J. Med. **241**:483-485, 1949.

or if the patient's comfort and well-being were bettered," they considered the result favorable. Corbin noted Schwabe and Leigh's[7] belief that objective tests are less reliable indices of change in paralysis agitans than the reports of patients and relatives. He considered a valuable criterion the patient's ability to carry out the routine chores of life. His determination of the effectiveness of trihexyphenidyl in patients with paralysis agitans was based on the patients' request for additional trihexyphenidyl or their statement that their condition had been improved by it, or that they preferred it to other medication. The evaluation of the efficacy of trihexyphenidyl in treatment of paralysis agitans in other clinical studies has been based either on the subjective report of the patients or on uncontrolled clinical observation.

PRESENT INVESTIGATION

In the present study we attempted to determine the relative efficacy of trihexyphenidyl in treatment of paralysis agitans (Parkinsonism) under controlled clinical observation, to compare chemotherapy with other forms of therapy of paralysis agitans, and to establish objective criteria for measuring changes under therapy.

Population.—Forty-one patients completed the study period. They were beneficiaries at the Veterans Administration Center at Bath, N. Y., and carried an established diagnosis of paralysis agitans. Ten patients lived in the hospital, and 31 lived in the domiciliary barracks. Thirty-six of the patients, divided into two groups, of 17 and 19, were under observation for the complete eight months of the study. Five patients were inducted into the experiment at various periods after the original 36 patients.

Drugs.—Three types of medication were used: trihexyphenidyl, stramonium, and a placebo. The drugs were prepared by the pharmacy in pink gelatin capsules in an effort to standardize the physical appearance of the medicament. Patients were never told what medication they were receiving, nor were they told when their medication was changed.

Exercises.—Each patient's performance on 16 tasks was studied. Records of the patient's efficiency in these tasks constituted an objective measure of change in muscular and mental control. The 16 exercises and the functions they measured are as follows:

A. Stylus hole	Hand tremor and rigidity
B. Small peg board	Finger dexterity
C. Large peg board	Shoulder movement
D. Bead stringing	Finger and hand dexterity
E. Board tapping	Wrist flexibility—extension-flexion
F. Wheel turning	Wrist flexibility—rotary motion
G. Dynamometer	Strength of grip
H. Foot tapping	Ankle flexibility—extension-flexion
J. Leg movements	Flexibility of lower extremities
K. Rail walking	Body balance
L. Stair walking	Control of muscle inertia
M. Frankel steps	Control of locomotion
N. Color naming	Control of vocal inertia
P. Word naming	Clearness of speech
Q. Code substitution	Associative cerebral processes
R. Arithmetic	Concentration

Subjective Evaluation of Patients.—Once a week each patient was interviewed and questioned on his progress. Each week he was asked 34 standard questions. The purpose of these questions was to establish a subjective evaluation of the patient's progress. The questions were so phrased that any ambiguity or inconsistency in the patient's self-evaluation might become apparent. This was accomplished by asking the same question in a different form. For example, a subject would be asked (Question 10): "Do you feel more relieved than usual? No different than usual? More excited and tense than usual?" Question 17 was: "Do you feel less nervous than usual? Normal? More nervous than usual?"

Procedure.—The patients were divided into two groups; the groups were equated for median chronological age, duration of illness, and type of paralysis agitans. All previous medication

7. Schwab, R. S., and Leigh, D.: Parpanit in the Treatment of Parkinson's Disease, J. A. M. A. **139**:629-634 (March 5) 1949.

was discontinued. One group, of 19 patients, was started on stramonium, while the other, of 17, was started on trihexyphenidyl.

Each patient's drug dose was increased daily until he reported toxic symptoms. The daily dose was then reduced to just below the point of toxicity, and this was considered the maintenance dose. After several weeks with no report of toxic symptoms, a higher dose would be tried again. If toxic symptoms returned, the dose was once more decreased to the lower maintenance dose. If no toxic symptom was reported, the patient was maintained on the higher dose. At all times an attempt was made to keep the patient on the highest dose possible short of toxic signs.[8]

In the second part of the experiment, all patients who started on stramonium were changed to trihexyphenidyl, and all patients who started on trihexyphenidyl were changed to stramonium. In the second part of the experiment, each patient was given the same number of capsules daily as he had received daily in the first part.

If a patient showed toxic signs under any degree of dosage, under any medication, the medication was reduced or eliminated temporarily, as the occasion required. Consistent with the comfort of the patient, attempts were continuous to maintain every patient on the maximum dose that he could tolerate. It was hoped to eliminate the possibility that patients were not receiving enough drugs for effective therapeusis.

The first period of drug therapy lasted 16 weeks. After the drug was changed, the patients continued 14 weeks on the new drug. The 5 patients who started in the experiment after the original 36 patients received no chemotherapy in the first part of the experiment. They did participate in all the exercises on a schedule similar to that of the original 36 patients. For them, this period varied from 6 to 14 weeks. In the second phase of the experiment, two of the five were brought up to maximum doses of stramonium, and three were maintained on trihexyphenidyl.

The patients were all seen once a week by a physician, who discussed their week's progress with them. At this conference, plans for the succeeding week's medication was determined. Changes in plans or medication could be instituted any time that a patient complained. He would bring his complaint to the nurse, who would immediately contact the physician. The case would be reviewed, and necessary changes in procedure would be instituted as needed. Once a week the patients were also given a short supportive psychotherapy session. At this session attempts were made to relieve anxieties that patients expressed. They were encouraged to participate fully in the therapy program that was set up for them. They were given encouragement about any progress they were making. Attention was given them that they ordinarily would not receive. Explanations were made that enabled them to have less anxiety about their condition.

Once a week the patients were asked to reply to the 34-question check list. The questions were read to them. The patients were required only to answer "yes" or "no" to some questions. To others the choice was "same," "better," or "worse."

No other supervision of the patients' activities was attempted. The patients were allowed to participate in all current activities in which they were interested. They participated in bowling, walking, going to movies, parties, and other social activities. They read books, magazines, and newspapers. One patient was a part-time secretary. Another supervised the activity of a recreation center. Some patients spent most of their free time sitting about doing nothing. Patients were encouraged to participate in any activity commensurate with their physical capabilities.

Results.—The change of efficiency in performing motor and mental tasks after 16 weeks of medication with trihexyphenidyl or stramonium was computed. The absolute level of performance varied considerably from patient to patient. All

8. One patient tolerated 35 grains (2.27 gm.) of stramonium daily. A second could tolerate only 10 grains (0.65 gm.) of stramonium daily. The number of patients who tolerated 15, 20, or 25 grains (0.98, 1.3, or 1.63 gm.) daily were approximately equal. Six patients tolerated 16 mg. of trihexyphenidyl daily. Seven tolerated only 14 mg. All patients could tolerate at least 10 mg. of trihexyphenidyl daily.

changes in performance were expressed as percentages of the initial level of performance for each patient for each exercise. (This was considered preferable to expressing change in absolute units of time, errors, and output.) In order that chance fluctuations in performance should be compensated for, the average of the first three trials in the drug period was compared with the average of the last three trials of the drug period. Table 1 A indicates that for both the 17 patients who were started on trihexyphenidyl and the 19 patients who were started on stramonium there was an increased average efficiency of performance in all five areas of function into which the 16 tasks could be categorized. The increase in efficiency averaged between 5.03 and 7.60% for all functions, except dexterity of the lower

TABLE 1.—*Mean Percentage Change in Efficiency*

A. From Beginning to End of a Drug Period (16 Weeks)

	Trihexyphenidyl		Stramonium		
Function Tested	Mean % Change	S. D.	Mean % Change	S. D.	Difference
Upper-extremity dexterity	+7.60	±15.26	+5.08	±14.52	2.52*
Lower-extremity dexterity	+28.65	±34.41	+31.84	±38.54	3.19*
Strength	+6.29	±13.54	+5.03	±13.94	1.26*
Walking	+5.06	±13.39	+5.31	±14.06	0.25*
Mental alertness	+7.49	±9.58	+6.37	±10.01	1.12*

B. On Changing Drugs

	Trihexyphenidyl to Stramonium		Stramonium to Trihexyphenidyl		
Function Tested	Mean % Change	S. D.	Mean % Change	S. D.	Difference
Upper-extremity dexterity	−3.96	±12.89	+0.73	±13.01	4.69*
Lower-extremity dexterity	−3.83	±12.57	−1.87	±12.03	1.96*
Strength	−2.65	±12.96	+1.65	±12.27	4.30*
Walking	−3.10	±13.01	+0.24	±12.93	3.34*
Mental alertness	+2.07	±7.11	+3.09	±9.34	1.02*

C. From Beginning to End of Experiment

	Began Trihexyphenidyl; Ended Stramonium		Began Stramonium; Ended Trihexyphenidyl		
Function Tested	Mean % Change	S. D.	Mean % Change	S. D.	Difference
Upper-extremity dexterity	+6.22	±14.23	+6.52	±13.95	0.30*
Lower-extremity dexterity	+22.19	±46.50	+33.19	±38.45	11.00*
Strength	+9.94	±14.31	+7.46	±13.85	2.48*
Walking	+6.74	±15.10	+5.48	±14.58	1.28*
Mental alertness	+12.73	±12.86	+12.93	±14.81	0.20*

* $P > 0.10$.

extremity. In the latter area, the average increase in efficiency was 28.65% for patients on trihexyphenidyl and 31.84% for the patients on stramonium. The differential increase of efficiency for the two drugs was not statistically significant for any functional area.

Whether the drugs tend to affect all activities proportionately or whether they have a differential effect was determined. Did trihexyphenidyl improve some functions more than stramonium? A rank-order correlation of the average improvement on any subtest for patients on trihexyphenidyl and the corresponding improvement for patients on stramonium was found to be 0.76 ± 0.058.

A comparison was made between the average performance on the last three weeks of a drug and the average performance during the first three weeks of the

new drug. The results, expressed as the mean percentage change from the average performance on the last three weeks of the first drug are given in Table 1 B. We find that patients who started on trihexyphenidyl therapy and were changed to stramonium therapy showed a regression in all areas except mental function. Patients who were started on stramonium and were then changed to trihexyphenidyl showed an average improvement in all areas except dexterity of the lower extremities. In all areas of function under study, patients who were on stramonium therapy and were changed to trihexyphenidyl therapy showed a comparatively slighter disruption of efficiency of performance than patients who were started on trihexyphenidyl and were changed to stramonium. The differences between the two groups, as given in the "Difference" column, are not statistically significant at the 5% level of confidence.

The percentage of improvement in efficiency from the beginning of the experiment to the end of the controlled period of drug therapy, 30 weeks later, is presented in Table 1 C. We find that for both groups of patients in all areas of function under study there was greater efficiency of performance at the end of the controlled drug period than at the beginning. The increases in efficiency varied from 5.48 to 33.19%.

The average percentage for tests showing an increase in efficiency, in any functional area, for patients who ended the experiment on stramonium did not differ significantly from the average percentage for tests showing an increase in efficiency, in the same functional area, for patients who ended the experiment on trihexyphenidyl. The obtained differences are not statistically significant at the 5% level of confidence.

A comparison of the efficiency of performance at the end of the first drug period with the efficiency of performance at the end of the second drug period is expressed as the average percentage improvement from the beginning of the experiment, as given in A and C of Table 1. We find that patients who were started on trihexyphenidyl and then were changed to stramonium showed poorer efficiency of the upper and lower extremities after the period of stramonium therapy than after the period of trihexyphenidyl therapy. They showed, however, increased strength, walking efficiency, and efficiency of mental function. Patients who started on stramonium and were then changed to trihexyphenidyl showed increased efficiency at the end of the period of trihexyphenidyl therapy in all functional areas.

The differences in efficiency from the end of the first drug period to the end of the second drug period are very small for both groups and are not statistically significant. The exceptions are the reduction in efficiency in lower-extremity dexterity for Group A at the end of the second drug period and the increase in efficiency in mental function for both groups at the end of the second drug period. But even these larger changes are not statistically reliable at an acceptable degree of probability.

The average change in efficiency for the five patients on the irregular schedule is given in Table 2. We find that up to the time they were placed on drug therapy their average increase in efficiency, with the exception of lower-extremity dexterity, approximated that which the two experimental groups had achieved by the end of their first experience with drug therapy. The level of efficiency achieved by these five patients at the end of their period of drug therapy was not significantly different from their level of performance achieved by practice on the exercises, but with no

chemotherapy. Their level of performance at the end of the experiment approximated that of the two experimental groups at the end of their second drug period with the exception of lower-extremity dexterity.

The standard questionnaire that all patients answered weekly can be divided into six categories. The questions regarded subjective evaluation of sleep activity, gastrointestinal activity, general autonomic activity, motor activity, general feeling

TABLE 2.—*Mean Percentage Change in Efficiency for Five Patients Who Started with No Chemotherapy and Were Later Placed on Chemotherapy*

	No Chemotherapy		Chemotherapy		
	Mean % Change	S. D.	Mean % Change	S. D.	Difference
Upper-extremity dexterity	+5.22	± 8.92	+ 6.83	± 9.04	1.61*
Lower-extremity dexterity	+7.39	±11.31	+ 6.44	±13.58	0.95*
Strength	+8.16	±13.16	+ 9.11	± 6.27	0.95*
Walking	+6.36	±12.74	+ 6.92	±13.81	0.56*
Mental function	+6.51	±11.23	+14.83	±16.94	8.32*

* $P > 0.10$.

TABLE 3.—*Subjective Evaluations Expressed as Percentages of the Responses**

	Trihexyphenidyl			Stramonium		
	Better	No Change	Worse	Better	No Change	Worse
Sleep activity	18	55	27	11	63	26
Gastrointestinal status	68	18	14	75	4	21
Autonomic activity	85	6	9	81	4	15
Motor activity	15	79	6	3	78	19
General tone	25	61	14	19	56	25
Mental tone	6	85	9	7	70	23
Weighted mean	50	38	12	46	34	20

* Percentage of responses expressing improvement, worsening, or no change.

TABLE 4.—*Subjective Evaluations Expressed as Mean Ratings*

	Trihexyphenidyl		Stramonium		
	Mean Rating	S. D.	Mean Rating	S. D.	Difference
Sleep activity	+0.41	±0.87	+0.39	±0.91	0.02*
Gastrointestinal status	+2.18	±2.06	+2.44	±1.99	0.16*
Autonomic activity	+5.14	±3.23	+4.26	±2.37	0.88*
Motor activity	+0.36	±1.27	−0.02	±1.88	0.38*
General tone	+0.02	±1.73	+0.08	±1.04	0.06*
Mental tone	+0.02	±0.69	−0.09	±0.88	0.11*

* $P > 0.10$.

tone, and general mental tone. For each patient the percentage of times he described himself as "better," "same," or "worse" in each category was calculated. The average percentage for the 17 patients on trihexyphenidyl and for the 19 patients on stramonium for the first 16 weeks of the experiment is given in Table 3.

There are some variations between the mean percentages for the group on trihexyphenidyl and the group on stramonium therapy. To test for the significance of the variations, the following statistical procedure was employed:

For each category for each patient, a point rating scale was constructed. For each patient there were computed the mean weekly rating for each category and the

mean rating for all categories. From these could be established, for each group of patients, the mean rating for each category for any drug period or fraction thereof. The results for the first 16 weeks are shown in Table 4.

A comparison of the differences in mean rating for the first 16 weeks between the trihexyphenidyl group and the stramonium group was made by Fisher's[9] *t* technique. For each category a *t* value of less than 1.0 was obtained. The observed differences (Table 4) are not statistically significant at the 5% level of confidence.

Of the five patients who started on exercise and other controlled activity without chemotherapy, 26% of the responses indicated a subjective evaluation of improvement in feeling or in motor ability, and 74% of the responses indicated no change during the drugless period. None of the responses given by these five patients in the drugless period indicated a worsening.

The differential effect of both stramonium and trihexyphenidyl on each of the six areas of subjective evaluation can be obtained from Tables 3 and 4. General autonomic activity and gastrointestinal status tended to be reported as improved. The patients reported experiencing the least effect on their mental tonus. Motor atcivity also was evaluated as showing little change. Sleep activity and general feeling tone were reported to be less affected than autonomic activity and gastrointestinal status, but more than motor activity and mental tonus.

The subjective evaluation of patients on the first three trials on any drug was compared with the subjective evaluation of the same patients on their first three trials on a new drug. The mean weighted percentages in the "better," "same," and "worse" columns for the group of patients who were started on trihexyphenidyl was not very different from those for the group of patients who were started on stramonium. This was confirmed by converting the judgments of the patients into point ratings. The mean of the ratings of the triphexyphenidyl group on the first three trials did not differ significantly from the mean of the stramonium group for the same period when tested by the *t* technique.

Similarly, on the first three trials of the second drug period, the two groups did not differ greatly in the average percentages in the "better," "same," and "worse" columns. The absence of a statistically significant difference is confirmed by converting the judgments into a point rating scale and comparing the mean group ratings by the *t* technique.

The judgments made on the first three trials of the first drug as compared with the judgments made on the first three trials of the second drug show some similarity of pattern. For both groups, the average percentage indicating a judgment of "worse" decreases, while the average percentage for the other judgments increase. The decrease is most marked in the group that started on stramonium and changed to trihexyphenidyl. As a test of the significance of the observed change, the judgments were converted into numerical ratings. The differences in meaning ratings between the two drug periods for homologous periods were small and were not significant at the 5% level of confidence.

COMMENT

After 16 weeks on chemotherapy, together with a planned program of physical therapy and psychotherapy, the patients in the two experimental groups showed

9. Fisher, R. A.: Statistical Methods for Research Workers, Edinburgh, Oliver & Boyd Ltd., 1944.

an objectively measurable improvement in motor dexterity, strength, walking, and mental alertness. Except for lower-extremity dexterity, the improvements were small. For lower-extremity dexterity, the probability that the improvement was due to chance is small. The probability is also small that the improvement in mental alertness shown by patients in the trihexyphenidyl group was due to chance. The improvement in mental alertness shown by the patients on stramonium therapy would have occurred by chance less than twice in 100 such studies. All other improvements were small as compared with the intragroup variability and cannot be considered statistically significant. That all mean changes were in the direction of improvement is worth noting.

There is reason to doubt that the improvements noted can be ascribed to the chemotherapy. The five patients who were under the same experimental regimen but who received no chemotherapy showed approximately the same amount of improvement in the objective tests in from 6 to 14 weeks. Percentagewise, the patients on a chemotherapy showed a greater improvement in the functional area of lower-extremity dexterity. It is doubtful whether this greater improvement can be related entirely to chemotherapy.

The 36 patients who were under chemotherapy had all been hospitalized or institutionalized for varying, but considerable, periods before the experiment began. Such patients, under the influence of institutional existence, tend to limit their activity, especially the lower extremities. In the experiment, they were forced to practice lower-extremity exercises. Improvement, when expressed either as an absolute amount or as a percentage of the regressed condition, is therefore relatively great. The patients not on chemotherapy had been continuously ambulatory. Their lower-extremity dexterity was not so markedly regressed at the time of their induction into the experiment. Exercise, therefore, did not create for them as great an increase in efficiency as it had done for the patients under chemotherapy.

If this reasoning is correct, it points up the importance of establishing a known base line before the effect of any kind of therapy can be evaluated. A patient who has been allowed to regress in any reversible function is more likely to show spectacular changes. The amount of change may be a function of the degree of deterioration rather than of the efficacy of the therapy under observation.

A qualitative analysis of the changes in the objective tests of patients under chemotherapy reveals that the objective criteria of age, duration of illness, and type of paralysis agitans were not good measures to be utilized in equating the groups. Intragroup differences for any variable were greater than intergroup differences. Age, duration of illness, and type of paralysis agitans did not seem to be related to the amount of improvement or lack of improvement on the objective tests. It was found that the amount of improvement in objective criteria tended to be a function of the degree of efficiency at which the patients were operating at the beginning of the experiment. Patients could be divided roughly into three groups. One group started poorly and progressed rapidly, although erratically. Another group started poorly and showed little or no progress. The third group exhibited the least regression initially and showed but little mean improvement.

An improved experimental method for the study of chemotherapies by means of objective tests then suggests itself. Patients should be exercised on the objective tests before chemotherapies are instituted. On the basis of the results obtained in the pretherapy period, groups equated on the basis of functional activity can be

established. If chemotherapies produce a differential improvement, it should be more apparent with such groups.

In the two groups under study in this experiment, neither trihexyphenidyl nor stramonium was superior in improving motor or mental efficiency as measured by objective tests. There was no differential effect of the two drugs when the criterion of the patient's subjective evaluation of his condition was used. The variability within each drug group was comparatively great, both on the objective tests and in the subjective evaluation. The differences between the means for the two groups are small compared with the intragroup variabilities. The small differences have little statistical significance. There are no specific trends. From Table 1 A we find that trihexyphenidyl was slightly superior in objective tests of upper-extremity dexterity, strength, and mental alertness. Stramonium was superior in objective tests of lower-extremity dexterity and walking. On the basis of subjective evaluation, we find in Table 4 that trihexyphenidyl was superior in its effects on sleep function, autonomic activity, motor activity, and mental tone. Stramonium was reported superior in its effects on gastrointestinal tone and general feeling tone. In every case the obtained differences can as easily be ascribed to other factors as to the differential effects of the drugs.

It is interesting to note that the mean level of efficiency on the objective tests at the end of 30 weeks is not significantly greater than at the end of 16 weeks. Only for mental activities is there a suggestion of continuous improvement with practice. An analysis of the individual practice curves, including the five patients who started with no chemotherapy, indicated that maximum efficiency tends to be approximated by the fourth to the sixth week of the experiment. After that, efficiency varies about a plateau level. The types of practice curves may have been a function of the small time given each week to the controlled exercises, the nature of the disease of the patients, or some other factor. An interesting comparison would be the effect of longer periods of exercise with no chemotherapy versus chemotherapy with no controlled exercise.

A differential effect of stramonium and trihexyphenidyl on individual motor activities was not indicated in the results of our objective tests. The correlation of average improvement with the two drugs was 0.76 ± 0.058. Motor and mental activities that were most improved in patients on trihexyphenidyl therapy tended to be most improved in patients on stramonium therapy.

It was found that refusal to use objective tests as indicative of efficiency of functional activity is not justified. Patients who did poorly on any of the objective tests did poorly in the daily motor activities of functional living. Although no numerical correlation of level of efficiency and skill in daily self-care was measured, it seemed notable that a significant relation existed. Patients who had the highest efficiency scores on the objective tests were most self-sufficient. Patients who required the greatest amount of auxiliary assistance in their daily routine activities scored the lowest on the objective tests.

There was no evidence to indicate that a patient's subjective evaluation of his condition reflected changes in his objective motor or mental efficiency. Correlations were computed for 12 patients chosen at random. For each patient a biserial correlation was computed between his mean weekly self-rating of his motor and mental condition and his average efficiency on the motor and mental tests. All correlations clustered about zero and showed little significance. This would not indi-

cate that the subject is unable to judge changes in efficiency. He is seemingly unable to apperceive reliably the small changes that occur with therapy in the case of paralysis agitans.

Subjective evaluation may be produced by psychological distortions and be misleading. Often those psychological distortions may seemingly affect the objective results; at other times they may result from the perception of transient changes in motor and mental efficiency and effect subjective evaluation. A patient who has not been seen by his doctor for several weeks will, in the normal course of events, have had several good and bad days in this interim. When asked how he is progressing, at the end of any period of time, he may claim to be better or worse. His judgment may be conditioned by his desire to please his therapist or by the time period in his cyclical course that he uses as a point of reference.

The patient's emotional status or self-concept should be significant in determining the level of efficiency at which the patient objectively operated. One patient in our series went from a deteriorated state to almost complete recovery and back to a dependent wheel-chair existence while on the same drug. Another patient reported a new ability to dress himself and perform other reacquired feats of self-care, while his objective tests showed no significant improvement. Another patient showed several cyclical episodes during the course of the experiment that had no temporal relation to any drug therapy. This patient would be entirely free of symptoms and perform excellently on the objective tests. In his opposite phase, he would show severe tremor, sialorrhea, festination, severe anxiety, and poor performance on the objective tests. These patients were all known to have post-encephalitis. What was the temporal causal relation between emotional state and objective efficiency cannot be determined from the evidence at hand. But the possibility of improved motor and mental performance following improvement in the patient's emotional tone must be considered.

Improvement or deterioration by subjective evaluation often results from what can be called a halo, or radiation, effect. Patients who by exercise manage to achieve improvement in a specific function tend to impute an improvement to other activities that is not objectively demonstrable. A patient who was able to effect an improvement in his mental-activity exercises tried valiantly to prove that he was vastly improved in all areas. His subjective evaluation was not consistent with his unimproved ability to perform on the objective tests or with his unimproved ability in self-care, as reported by the nursing and attendant staff. The patient cited above who reacquired the ability to dress himself and perform other feats of self-care showed no significant improvement on the objective tests. He had been encouraged by a nurse to attempt to dress himself. He was told that the exercise regimen had probably brought him to the level of self-care. His attempt and consequent success so buoyed him that he subjectively extended his improvements to many other activities. This could not be established objectively. Another patient was subject from time to time to arthritic pain in his lower extremities. When this occurred, he would report deterioration in his motor and mental activity. Objective tests usually failed to note a decrease in motor or mental efficiency.

CONCLUSIONS

A concerted regimen of therapy, including chemotherapy, physical therapy, and psychotherapy, can effect improvement in many cases of paralysis agitans (Parkinsonism).

Trihexyphenidyl (artane*) has not been demonstrated to be superior to stramonium as a chemotherapy for paralysis agitans. There seems to be little differential effect of the two drugs.

Effects attributed to chemotherapy are often the result of physical therapy and psychotherapy.

Objective tests are useful in evaluating improvement in paralysis agitans and are probably more reliable than subjective evaluations.

An improved method of studying the effect of chemotherapy in paralysis agitans by utilizing a functionally equated homogenous group is suggested.

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EXPERIMENTAL CEREBELLAR SEIZURES

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WHILE the clinical manifestations and experimental production of epileptic seizures of cerebral origin are well known and the electrical changes associated with such seizures have been extensively investigated, the concept of "cerebellar seizures," or "cerebellar fits," is an obscure one. Credit for the first description of a so-called cerebellar seizure is given to Wurffbain [1] who in 1691 described a case of cerebellar tumor with severe seizures of head retraction. In 1871 Hughlings Jackson [2] described a case of tumor of the middle lobe of the cerebellum with seizures characterized by clenching of the hands, flexion of the forearms, arching of the back and neck, and extension of the legs and feet. Since then, this type of seizure has become known generally as a "cerebellar fit," and a number of instances occurring with tumors of the posterior fossa have been reported.

Not all seizures associated with tumors of the posterior fossa, however, are of this type. Collier [3] in 1904, described focal jerkings of the arm and face and generalized convulsions in cases of tumor of the brain stem and of the cerebellum. Other reports have also pointed out the occurrence of generalized clonic attacks in cases of cerebellar tumor. In 1940 Webster and Weinberger [4] reviewed 158 cases of verified intracerebellar tumors and found segmental clonic, generalized clonic, generalized tonic, and syncopal attacks. Penfield and Erickson [5] in 164 cases of

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4. Webster, J. E., and Weinberger, L. M.: Convulsions Associated with Tumors of the Cerebellum: Clinical and Pathophysiologic Features, Arch. Neurol. & Psychiat. **43**:1163-1184 (June) 1940.

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infratentorial tumor, found a variety of forms of attack, including epileptic seizures of the cerebral type, facial twitching, focal clonic movements, "bulbar palsy," vertigo, syncope, paresthesias, and tonic seizures. Of 247 patients at the Johns Hopkins Hospital having tumors of the posterior fossa 12 exhibited seizures of some form. Five had only fainting attacks. Three had tonic seizures, two had focal clonic twitchings of the face; one had tonic-clonic attacks involving the right side, and one had generalized tonic-clonic seizures. Penfield and Erickson [5] point out that attacks which occur in cases of subtentorial tumor are usually not epileptic seizures of the cerebral type unless complicating factors, such as cerebral metastases from a cerebellar medulloblastoma, are present.

The pathogenesis of the so-called cerebellar fit is not clearly known, although it has generally been assumed to be on the basis of a temporary physiologic decerebration. Penfield and Erickson [5] stated that the term "cerebellar seizure" is a misnomer; that the attack has nothing to do with the cerebellum itself and may be considered either as a release phenomenon due to temporary ischemic transection of the midbrain or as an epileptic seizure whose origin is spontaneous neuronal discharge within centers in the upper part of the pons or the lower portion of the midbrain. Webster and Weinberger [4] stated the belief that all types of epileptic seizures which occur in association with cerebellar tumors can be explained on the basis of decortication produced by temporary cortical ischemia resulting from transitory alterations in the intracranial pressure. Grinker and Bucy [6] stated that these attacks of extension resemble temporary states of decerebration and represent either release of lower structures from inhibition of the midbrain or stimulation of mechanisms augmenting postural tone.

Clinical observations appear to have added little to the problem as to whether a form of epileptic seizure may actually arise from the cerebellum. Experimental evidence, also, is scanty. Clark, Ward, and Payne [7] have described movements in cats which occur after electrical stimulation of the cerebellum, after mechanical injury to the cerebellum (introduction of a needle), and at the end of a clonic fit produced by electrical stimulation of the cerebrum. These motor phenomena are described as a series of relatively slow movements occurring in a definite sequence, lasting several minutes, and involving the various parts of the animal in what appears to be changes in posture. No changes have been described in the cerebellar electroencephalogram associated with these movements.[8] Miller,[9] in 1926,

6. Grinker, R. R., and Bucy, P. C.: Neurology, Ed. 4, Springfield, Ill., Charles C Thomas, Publisher, 1949.

7. Clark, S. L.: Motor Seizures Accompanying Small Cerebellar Lesions in Cats, J. Comp. Neurol. **71**:41-57, 1939; Responses Following Electrical Stimulation of the Cerebellar Cortex in the Normal Cat, J. Neurophysiol. **2**:19-35, 1939. Payne, J. T.; Clark, S. L.; Ward, J. W., and Cowden, F. E.: Atypical Seizures Elicited by Electrical Stimulation of the Cerebrum in the Cat, Arch. Neurol. & Psychiat. **49**:244-253 (Feb.) 1943. Ward, J. W., and Clark, S. L.: Convulsions Produced by Electrical Stimulation of the Cerebral Cortex of Unanesthetized Cats, ibid. **39**:1213-1227 (June) 1938.

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9. Miller, F. R.: Action of Strychnine on the Cerebellar Cortex, Tr. Roy. Soc. Canada **20**:239-240, 1926.

reported his applying 1% strychnine nitrate to the surface of the cerebellum of cats and observing extensor tonus and clonic contractions affecting mainly the ipsilateral hindleg, but also to some degree the contralateral hindleg and both forelegs.

In several previous communications, we [10] have described the effects of various physical and chemical agents on the electrocerebellogram of the cat. In the course

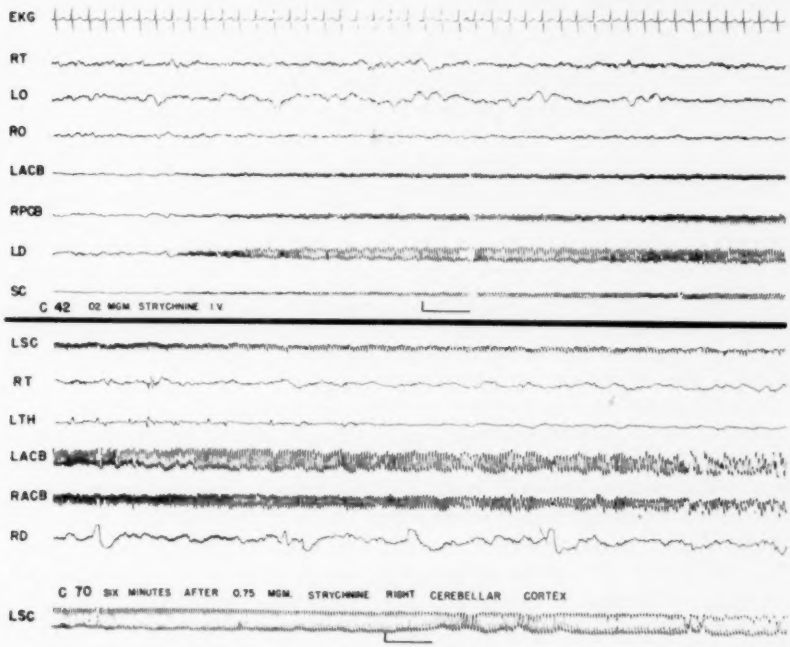

Fig. 1.—Electrocorticograms and electrocerebellograms of two cats. The upper group of tracings shows the effect of 0.02 mg. of strychnine sulfate given intravenously, and the lower group demonstrates the response obtained six minutes after 0.75 mg. of strychnine sulfate was injected into the right cerebellar cortex. The development of high-voltage synchronous rhythmical waves from the cerebellum and spinal cord is apparent. Abbreviations used in this and in subsequent figures are as follows:

DC, distal segment of transected spinal cord; *EKG*, electrocardiogram; *LAC* and *LACB*, cortex of left anterior cerebellar lobe; *LD*, left dentate nucleus; *LF*, left frontal cortex; *LO*, left occipital cortex; *LP*, left parietal cortex; *LPC*, cortex of left posterior cerebellar lobe; *LSC*, lumbar portion of spinal cord; *LT*, left temporal cortex; *LTh*, left thalamus; *PC*, proximal segment of transected spinal cord; *RAC* and *RACB*, cortex of right anterior cerebellar lobe; *RD*, right dentate nucleus; *RF*, right frontal cortex; *RO*, right occipital cortex; *RP*, right parietal cortex; *RPC* and *RPCB*, cortex of right posterior cerebellar lobe; *RT*, right temporal cortex, and *SC*, spinal cord.

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10. (*a*) Johnson, H. C.; Browne, K. M.; Markham, J. W., and Walker, A. E.: Effect of Strychnine on the Cat's Electrocerebellogram, Proc. Soc. Exper. Biol. & Med. **73**:97-99, 1950. (*b*) Markham, J. W.; Browne, K. M.; Johnson, H. C., and Walker, A. E.: Convulsive Patterns in Cerebellum and Brain Stem, A. Res. Nerv. & Ment. Dis., Proc. (1950), to be published; (*c*) Rhombencephalic Convulsive Activity, Bull. Johns Hopkins Hosp. **89**:442-467, 1951.

of these experiments it was found that strychnine causes pronounced changes in the electrocerebellogram. When strychnine is applied topically to the cerebellum, injected into the cerebellar cortex or cerebellar nuclei, or given intravenously, the changes in the electrocerebellogram are characterized by the appearance of rhythmical waves with a frequency of 10 to 30 per second and an amplitude of 100 to 400 μv, occurring in periodic discharges (Fig. 1). When the drug is injected intravenously or into the region of the cerebellar nuclei, amounts of 0.018 to 0.022 mg. per kilogram of body weight will in most instances result in the rhythmical discharges. When strychnine is injected into the cerebellar cortex, approximately 0.10 mg. per kilogram of body weight is the necessary dose. In general, when the strychnine was injected in amounts just sufficient to produce a response, the electrical changes appeared within one to two minutes. These rhythmical waves occurred in periodic discharges of 30 seconds' to 3 minutes' duration, recurring at intervals of 1 to 3 minutes for 30 minutes to 1 hour.

Recordings were generally taken from the anterior and posterior surfaces of the two cerebellar hemispheres and from the region of the dentate nuclei. In most experiments the discharge appeared from all areas of the cerebellum simultaneously. Frequently, however, the amplitude was higher from the dentate nucleus and the anterior surface of the cerebellum. In two animals the changes appeared first from these regions. These changes in the electrocerebellogram appear in the decerebrate animal, as well as from the intact brain.

In a number of experiments, recordings were made from the spinal cord, medulla, and thalamus simultaneously with the cerebellar recording. While a systematic examination of the thalamus has not been made, this type of discharge from the cerebellum appears to have no effect on the thalamus. Recordings from the medulla and spinal cord show the same rhythmical discharge as that from the cerebellum.

Since clinical cerebral fits are commonly associated with electrocorticographic changes, it is natural to assume that if a seizure arises from the cerebellum, it ought to be associated with changes in the electrocerebellogram. An analysis of the rhythmical wave pattern obtained from the cerebellum after its stimulation with strychnine reveals that it has certain similarities to the electrical discharge of the cerebrum which is associated with a generalized tonic-clonic seizure. It starts and stops suddenly and then recurs at irregular intervals. Each is frequently characterized by an interseizure type of pattern. Each is readily stopped by the administration of phenobarbital, pentobarbital sodium, and ether. Because the animals used in these experiments were curarized to prevent muscle artifacts, the motor phenomena concomitant with the cerebellar discharges could not be studied. Proceeding on the hypothesis that the electrical activity which had been observed from the cerebellum after the administration of strychnine might be the electrical manifestation of a "cerebellar fit," we carried out the following experiments in order to observe the type of motor activity associated with the electric pattern.

METHOD

The details of the experimental technique have been described in other communications.[10] In the present group of experiments, 30 healthy adult cats were used for acute observations. When strychnine was to be injected into the cerebellum, a trephine opening was made over

the cerebellum several days previously with the animal under ether anesthesia and with the use of aseptic technique. In certain animals a transection of the midthoracic portion of the cord was done under aseptic conditions one to several days previously. The acute technical procedures were carried out with the use of local infiltration anesthesia, and at the conclusion of the observations the animals were painlessly killed.

RESULTS

When a 1% solution of strychnine sulfate is injected intravenously into the cat in amounts varying from 0.05 to 1.0 mg., the well-known picture of strychnine tetanus develops. This observation was made on four cats in these experiments. Within 30 seconds after the injection of strychnine, the cat exhibited a generalized tonic seizure. There were extension of all the limbs, opisthotonos, and arching of the back. A few clonic movements might be observed. With the larger doses there was apnea associated with the severe tonic state, and the animal died within several minutes. With the smaller doses the tonic seizure might repeat itself several times with intervening periods of hyperpnea, from which the animal might recover in 30 to 45 minutes.

In a group of four cats, strychnine was injected into the cerebellum in amounts varying from 0.1 to 0.3 mg. The type of motor activity seen in these animals was quite different from that which followed the intravenous injection of strychnine. Within one to two minutes after the injection of strychnine into the cerebellum, the animal exhibited motor activity, characterized by regular, rapid running movements of the extremities. At the same time the animal might roll quickly and violently over and over. This might stop after 10 to 15 seconds, to start again with the fast running movements. After this activity had continued from 2 to 15 minutes, a sudden generalized tetanus developed. The following protocol describes the usual activity seen:

CAT 131.—March 14, 1950: Ether anesthesia; 5-mm. trephine opening made in midline over cerebellum.

March 15: Animal appears normal.

10:00 a. m.: Without anesthesia, a No. 25 needle inserted through skin and trephine opening to depth of 1.5 cm. into cerebellum and 0.02 cc. of 1% strychnine sulfate (0.2 mg.) injected. Immediate onset of wild clawing, running movements of all extremities, followed by fast rolling over and over of entire body, lasting 45 seconds.

10:01 a. m.: Marked extensor spasm of all extremities.

10:02 a. m.: Animal dead.

The same experiment was carried out on the decerebrate cat, with similar results.

Similar observations on the motor manifestations following the intravenous and intracerebellar injections of strychnine were also made on cats with chronic transection of the midthoracic portion of the spinal cord. When strychnine was injected intravenously into four such animals, they had the same type of tonic seizure as that seen in the intact animal. In seven cats with sections of the cord, strychnine was injected into the cerebellum in amounts ranging from 0.05 to 0.20 mg. Within 15 to 30 seconds the animal exhibited the regular, fast running movements of the forelegs and the violent rolling over and over. The hindlegs remained motionless during this activity, which might last for several minutes or as long as 15 minutes. This movement of the forelegs and trunk was suddenly terminated

by a generalized tonic seizure involving the entire body and resembling in all respects the seizures observed after the intravenous injection of strychnine. The following protocol illustrates this:

Cat 124.—March 7, 1950: Ether anesthesia; 5-mm. trephine opening made in suboccipital region over midline of cerebellum; midthoracic laminectomy and complete transection of cord.

March 8: Animal in good condition; sitting up. No movement in hindlegs.

9:40 a. m.: Without anesthesia, a No. 25 needle inserted through suboccipital trephine to depth of 1.5 cm.; 0.02 cc. of 1% strychnine sulfate (0.2 mg.) injected into cerebellum.

9:40, 15″: Clawing movements of left forepaw.

9:40, 25″: Clawing movements of both upper limbs.

9:40, 30″: Wild, fast running movements of both upper limbs; rolling over.

9:41, 15″: Rapid running or swimming movements continued in forelegs; neck flexed; neck starting to go into opisthotonos.

9:41, 45″: Frothing at mouth; forelegs starting to go into slow tonic extension with flexion at wrists.

9:42, 15″: Breathing stopped; artificial respiration.

9:42, 30″: Hindlegs in marked extension.

9:42, 45″: Heart very slow.

9:44 a. m.: Animal dead.

The sequence of appearance of the motor activity in an animal with transection of the spinal cord corresponds to the pattern of electrical activity. In this type of preparation, after the cerebellar injection of strychnine, the rhythmical electrical discharge appears first in the cerebellum or cerebellum and proximal segment of the cord, just as the motor response is first evident proximal to the section of the cord. After there has been time for systemic absorption of the strychnine, the electrical discharge appears also in the distal segment of the cord (Fig. 2).

It is known that chlorophenothane U. S. P. (dichlorodiphenyltrichloroethane; DDT) causes a marked degeneration of the cerebellar parenchyma, especially the Purkinje cells.[11] To test the hypothesis that these fits are cerebellar in origin, five cats were fed a diet containing 800 mg. of chlorophenothane daily. Within several days these animals exhibited generalized tremor and ataxia, which was so severe in some of the cats that they were unable to walk. In one such animal 0.15 mg. of strychnine sulfate was injected into the cerebellum. The usual running movements and rolling over did not develop, but in two minutes there was severe generalized tonic extension, with death in four minutes. Electrocerebellograms were made on the other four cats when the toxic effects of chlorophenothane became manifest. The spontaneous records of these animals showed some increase in voltage, with some irregular waves. In a normal cat, 0.05 to 0.10 mg. of strychnine sulfate given intravenously, or 0.1 to 0.3 mg. injected into the dentate nucleus, usually will result in high-amplitude rhythmical waves in the electrocerebellogram. In none of the cats fed chlorophenothane could these changes in the electrocerebellogram be produced even with amounts of strychnine as large as 2.6 mg. given intravenously and 1.2 mg. injected into the cerebellum (Fig. 3). Histologically there were severe destructive changes in the Purkinje cells and in the neurones of the cerebellar nuclei.

11. Haymaker, W.; Ginzler, A. M., and Ferguson, R. L.: Toxic Effects of Prolonged Ingestion of D.D.T. on Dogs with Special Reference to Lesions in the Brain, Am. J. M. Sc. **212**:423-431, 1946.

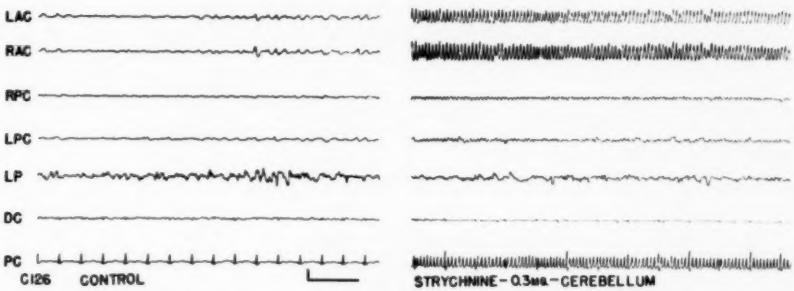

Fig. 2.—Electrograms of a cat three days after midthoracic transection of the cord. The tracings at the left were taken before any medication, and those at the right were taken 50 minutes after the injection of 0.3 mg. of strychnine sulfate, in three doses, into the left cerebellar hemisphere. The cerebellum and the proximal portion of the spinal cord show the usual rhythmical activity, whereas the recording from the distal segment of the cord remains unchanged. A subsequent intravenous injection of strychnine induced similar activity in the distal segment of the spinal cord. The horizontal line at the base indicates an interval of one second, and the vertical line, a calibration of 200 μv.

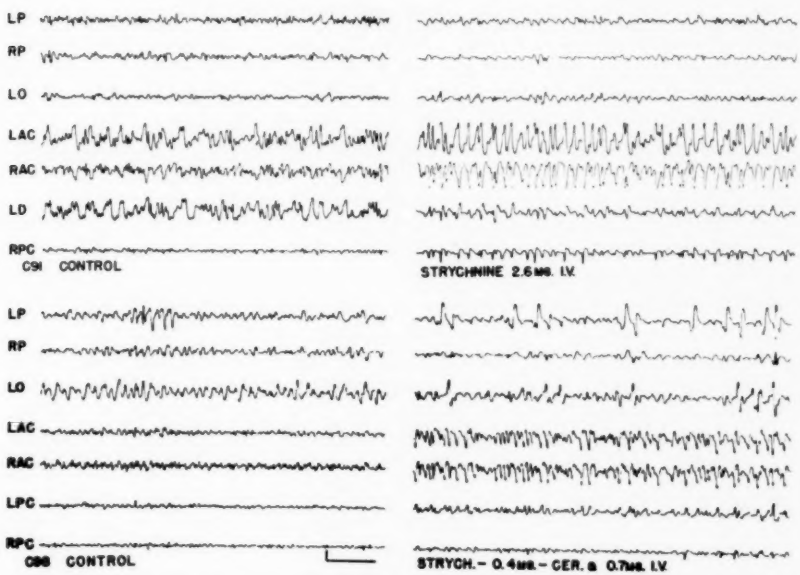

Fig. 3.—Electrograms of two cats which received 800 mg. of chlorophenothane (DDT) orally each day—Cat C91, for four days, and Cat C96, for two weeks. At the time of these recordings the animals showed severe ataxia and tremor. The control records, before the administration of any strychnine, show a somewhat higher-voltage record from the cerebellum than is usually obtained from the normal animal. In Cat C 91 after the intravenous administration of as much as 2.6 mg. of strychnine sulfate and in Cat C 96, after 0.4 mg. had been given into the cerebellum and 0.7 mg. intravenously, the usual rhythmical wave form could not be obtained. The horizontal line at the base represents a period of one second, and the vertical line, a calibration of 200 μv.

COMMENT

These experiments have demonstrated a certain type of motor phenomenon seen in the cat, after the injection of strychnine into the cerebellum, which differs from that seen after the intravenous injection. If this motor response is secondary to stimulation of the cerebellum and is dependent upon cerebellar activity, it might properly be called a "cerebellar fit."

The exact origin of the high-amplitude rhythmical activity in the electrocerebellogram which occurs after an injection of strychnine is not clear. In a previous communication [10b] this response has been referred to as a pattern of brain stem-cerebellar convulsive activity, since it may occur in the cerebellum, brain stem, or spinal cord in practically identical form, although not necessarily simultaneously from all three regions. While the brain stem-cerebellar activity is often associated with similar activity of the spinal cord, it may occur independently. Whether the rhythmical activity arises entirely independently in the cerebellar neurones, or whether it is dependent upon some connection with the brain stem, such as a reticular internuncial system, is difficult to say.

Nor is it possible at the present time to ascribe the type of seizure occurring after cerebellar injection of strychnine to an independent cerebellar activity. The motor activity following the intravenous injection of strychnine can probably be ascribed largely to a spinal tetanus. The same activity appearing at the end of a "cerebellar fit" after cerebellar injection is probably secondary to the systemic absorption of strychnine, with its resulting effect on the spinal cord. The results in the animals with spinal transections would indicate that the cord is probably not responsible for the onset of the initial motor response following the cerebellar injection of strychnine. In such an animal the electrical discharge appeared first in the cerebellum, or the cerebellum and proximal segment of the cord, and only after there had been time for systemic absorption of the strychnine did the distal segment of the cord discharge. If the cerebellar discharge and motor activity after cerebellar injection were secondary to spinal-cord impulses alone, one would expect the distal and the proximal segments of the cord to be affected simultaneously.

After severe damage to the cerebellum by the ingestion of chlorophenothane, neither the rhythmical electrical wave form nor the usual motor activity could be brought out by the injection of strychnine. This, of course, does not prove that the seizure originates in the cerebellum, but it is suggestive evidence that the cerebellum is at least necessary for the activity.

In view of the fact that the electrical pattern and motor activity of a generalized cerebral seizure are relatively the same whether initiated by electrical or chemical stimulation, the question arises whether the cerebellar response is specific for strychnine or whether it is a pattern which can be evoked by other methods of stimulation. Electrical stimulation of the cerebellum has generally been ineffective in producing changes in the electrocerebellogram. In several instances, however, a strychnine-like rhythmical discharge has been induced. Such a response was obtained from one isolated encephalon preparation, in which a 10-volt, 60-cycle current was passed between electrodes placed, respectively, in the left cruciate gyrus and the right posterior cerebellar lobe for 10 seconds. In another experiment, on an intact cat, stimulation (30 volts, 60 cycles) of the left cruciate gyrus for 15 seconds was followed in 20 seconds by the sudden onset of large regular, sharp waves of 200 to 240 μv at a frequency of 14 cps from the right anterior

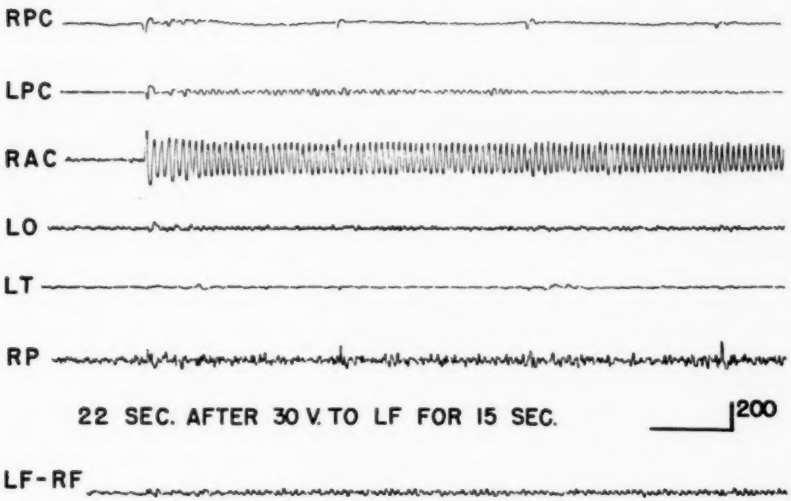

Fig. 4.—In Cat 173 an electrical stimulus of 30 volts and 60 cycles was applied to the left cruciate gyrus for 15 seconds. Twenty-two seconds later this was followed by the sudden onset of large regular, sharp waves of 200 to 240 μv. at 14 per second from the right anterior cerebellar lobe, lasting about 20 seconds. The appearance is like that of the strychnine-induced discharge. The horizontal line at the base represents an interval of one second, and the vertical line, a calibration of 200 μv.

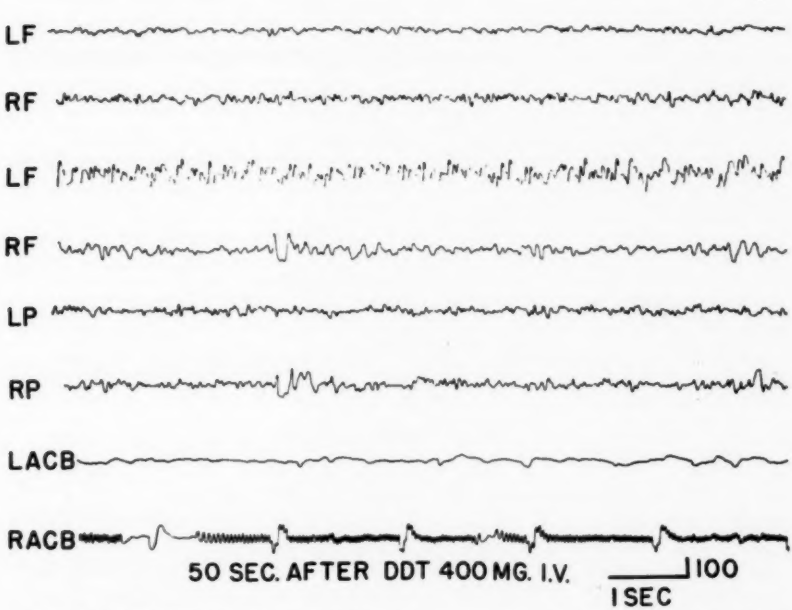

Fig. 5.—The monkey was given a continuous slow intravenous injection of a 5% suspension of chlorophenothane. The electrogram was taken 50 seconds after the onset of the injection, when 400 mg. had been given. The rhythmical wave form recorded from the right anterior cerebellar lobe resembles that seen after the injection of strychnine.

cerebellar lobe, lasting for about 20 seconds (Fig. 4). In another report [10c] we have described in detail the effects on the electrical activity of the cerebellum of a number of drugs variously administered. These include caffeine and sodium benzoate U. S. P., niketharnide, ephedrine, picrotoxin, acetylcholine, and physostigmine. In no instance did rhythmical discharges appear. In the decerebrate cat penicillin in amounts of 10,000 units or more injected into the cerebellum has been followed within five minutes by slow, twisting movements of the head and wild movements of the limbs, particularly the contralateral hindlimb. Electroencephalographic studies of such preparations immobilized by curare did not reveal significant alterations in the electrocerebellogram. On several occasions spontaneous "strychnine" patterns have been observed in the cerebellum before any strychnine has been given. It is possible that curare or procaine used in the preparation of the animal was responsible, but we have been unable to demonstrate an epileptogenic effect of these drugs when given intravenously. The intramuscular administration of 70 to 100 mg. of procaine hydrochloride has caused such changes of short duration. In one experiment on the macaque monkey, chlorophenothane given intravenously caused the same changes in the electrical pattern

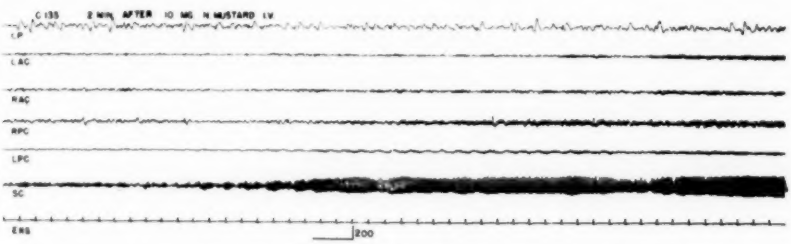

Fig. 6.—Electrograms of a cat taken two minutes after the intravenous injection of 10 mg. of nitrogen mustard (methyl-*bis*[β-chloroethyl]-amine). The wave form recorded from the cerebellum and spinal cord is like that observed after the injection of strychnine. The horizontal line at the base represents an interval of one second, and the vertical line, a calibration of 200 μv.

of the cerebellum as those obtained with strychnine (Fig. 5). In one cat, nitrogen mustard (methyl-*bis* or-*tris*[β-chloroethyl]-amine) given intravenously resulted in an electrocerebellogram similar to that seen after strychnine (Fig. 6). It would appear, then, that the cerebellar activity may be modified by many agents to the rapid, rhythmical, high-amplitude pattern described. This may well represent the convulsive cerebellar activity and be associated with a true cerebellar seizure.

SUMMARY

Changes in the electrocerebellogram following the intravenous and intracerebellar injections of strychnine are described. The motor responses obtained in the noncurarized cat after similar injection of strychnine are also described. After the intracerebellar injection of strychnine, the cat shows a rapid and violent rolling over and over of its body, associated with rapid running movements of the extremities. This motor activity is thought to be associated with the changes observed in the electrocerebellogram. Evidence is discussed for the suggestion that this might be called a cerebellar seizure.

RIBOSURIA

A Clinical Test for Muscular Dystrophy

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THERE has always been difficulty in differentiating and in classifying the various diseases in which motor weakness and muscular wasting are the prime symptoms. The seemingly endless variations and gradations of types have led many investigators to combine groups of them under the general heading of heredodegenerative disease, rather than pursue the fruitless task of making a specific diagnosis. This is reasonable, as, with two notable exceptions, no specific treatment has proved effective and the diagnosis is often nothing more than a glossary of eminent neurologists of the past.

Laboratory tests, including determinations of electrical reactions, creatine excretion, and tolerance, have occasionally proved helpful but are not specific for one group as opposed to another. Muscle biopsy is often inconclusive. Even necropsy may leave the diagnosis in doubt.

In a study of urine in several cases of pseudohypertrophic muscular dystrophy, Minot [1] noted that reduction was invariably obtained when 8 to 10 drops of urine was heated in a boiling water bath for 45 minutes with 5 cc. of Benedict's qualitative solution.[2] The substance producing this reduction was found to be *d*-ribose, which is excreted as a phosphorus-containing complex.

In 1907 Cassirer and Bamberger [3] reported a case of anterior crural neuritis in an alcoholic patient with cardiac disease who showed persistent pentosuria (exact pentose not identified) even after a fruit-free diet, but Wilson [4] and others have failed to confirm this finding.

During the past years we have examined the urines of many patients with acute and chronic muscular wasting, as well as various neurological and muscular diseases more distantly related in their symptomatology to pseudohypertrophic muscular dystrophy. The vast majority of patients were selected from the hospital and out-

From the Departments of Psychiatry and Biochemistry, Vanderbilt University School of Medicine.

1. Minot, A. S.: Frank, H., and Dziewiatkowski, D.: Occurrence of Pentose- and Phosphorus-Containing Complexes in the Urine of Patients with Progressive Muscular Dystrophy, Arch. Biochem. **20**:394, 1949.

2. Benedict's qualitative reagent contains, per 1,000 cc., 12.3 gm. crystalline copper sulfate, 173 gm. sodium citrate and 100 gm. anhydrous sodium carbonate.

3. Cassirer and Bamberger: Ein Fall von doppelseitiger Neuritis des N. cruralis bei Pentosurie, Deutsche med. Wchnschr. **33**:886, 1907.

4. Wilson, S. A. K.: Neurology, Baltimore, Williams & Wilkins Company, 1904, p. 339.

patient departments of Vanderbilt University Hospital, nearly all of whom were seen by one of us, and the diagnosis was made from clinical findings.

PROCEDURE

After the patient had been on a diet free of fruit for one day, the first morning specimen of urine was obtained and preserved with a few crystals of thymol. The specimen of untreated urine was first subjected to a simple screening reduction test with Benedict's qualitative sugar reagent run in the usual manner, except that heating in a boiling water bath was continued for 45 minutes. If no indication of reduction of copper was apparent after this length of time, the sample of urine was dismissed as negative for reducing sugar. Urines containing pentose complexes cause a reduction of copper on prolonged heating with Benedict's solution, but so also do urines with a high content of creatinine or uric acid, glycuronates, etc. Thus, a positive reaction to the screening test means only that the specimen deserves further study. For this, 30 to 40 cc. of urine is mixed with one-half this volume of a freshly prepared 40% suspension of washed yeast and allowed to stand, with occasional mixing, for 15 minutes at room temperature. At the end of this time sufficient 1 N sulfuric acid is added so that the final dilution of the added acid will be aproximately 0.02 N. Then 1.5 gm. of Lloyd's reagent is added for each 10 cc. of original urine used and the mixture shaken for two minutes and then centrifuged or filtered. This procedure, which is essentially that of Van Slyke and Hawkins,[5] removes glucose and various other interfering substances. A few drops (8 to 10) of clear filtrate are again tested by prolonged heating with Benedict's qualitative sugar reagent. Since neither free pentose nor the complexes of interest in the present study are removed by the treatment with yeast and Lloyd's reagent, the absence of reduction at this point indicates that they are not present in detectable amounts. With the majority of urines a positive reaction in the reduction test at this stage is indicative of pentose. Because an occasional urine is encountered, however, which contains sufficient glycuronate to yield a confusing reduction, it is far safer to withhold any positive conclusion until the phenylhydrazine test has been made. To accomplish this, the remainder of the treated urine, 20 to 30 cc., is mixed in a large test tube with about one-half its volume of a freshly prepared solution containing 1 gm. of phenylhydrazine hydrochloride and 4 gm. of sodium acetate dissolved in 20 cc. of 10% acetic acid. The tube is heated in a boiling water bath for 45 minutes; the heat is then turned off, and the contents of the tube are allowed to cool slowly in the hot bath and to stand at least overnight. If pentose is present, microscopic examination of a drop of the sediment which settles in the tube will usually reveal unmistakable yellow crystalline osazones, admixed with varying amounts of amorphous debris. This constitutes a positive result, and it is entirely optional whether or not one goes further and recrystallizes the osazones until they are free from other insoluble debris. The size and pattern of the crystals varies according to the amount of pentose present, the state of purification, and the rate of cooling. The most characteristic form, however, is that of shiny, sharp, somewhat flattened yellow needles, which tend to form rosettes, with the needles radiating in several planes from a central point.

One source of possible error which must be borne in mind is transient alimentary pentosuria, which may result from eating fruit. Pentose from such a source would, of course, be isolated as a pentosazone and so give a false positive result. This can easily be avoided by placing the patient on a fruit-free diet for a day or two before the urinary tests are made. The pentose constantly present in an occasional rare case of essential pentosuria has been shown by Greenwald[6] to be *l*-xyloketose. Lasker and Enklewitz[7] have shown that this sugar readily reduces Benedict's solution at a low temperature (55 C.)—a characteristic which would serve to differentiate it from the slowly reducing properties of the pentose complexes which occur in muscular dystrophy.

5. Van Slyke, D. D., and Hawkins, J. A.: Gasometric Determination of Fermentable Sugar in Blood and Urine, J. Biol. Chem. **79**:739, 1926.

6. Greenwald, I.: Nature of the Sugar in 4 Cases of Pentosuria, J. Biol. Chem. **88**:1, 1930; Correction, ibid. **89**:501, 1930.

7. Lasker, M., and Enklewitz, M.: A Simple Method for the Detection and Estimation of L-Xyloketose in Urine, J. Biol. Chem. **101**:289, 1933.

I. 8-10 drops of urine in 5 cc. qualitative Benedict's solution; heat 45 minutes in boiling water bath

Reduction	No reduction
Suggestive positive test	Negative test

↘

II. Treat with yeast and Lloyd's reagent and repeat (I)

Reduction	No reduction
Presumptive positive test	Negative test

↘

III. Phenylhydrazine

Typical crystals	Atypical crystals or Large amount of amorphous debris
Completed positive test	

↙

Recrystallize

Typical crystals	No crystals or atypical white (colorless) crystals
Completed positive test	Negative test

RESULTS

A positive reaction for ribose was found in the following conditions:

Progressive muscular dystrophy—all types (26 cases)
- Pseudohypertrophic muscular dystrophy
- Facioscapulohumeral muscular dystrophy
- "Late forms"
- Gower's distal type

Dystrophia mytonica (6 cases)
Myotonia congenita (5 cases)
Amyotonia congenita (3 cases)

In many such cases, repeated examination of the patient's urine always yielded positive results.

In one case of plasma cell myeloma with pronounced muscular wasting, ribose was found, but the patient died prior to repetition of the test.

Negative reactions were obtained in all other conditions, including the following diseases:

Amyotrophic lateral sclerosis
Cerebellar ataxia
Multiple sclerosis
Myasthenia gravis
Essential polyangiitis (periarteritis nodosa)
Familial periodic paralysis
Progressive neuropathic (peroneal) muscular atrophy (Charcot-Marie-Tooth disease)
Peripheral neuritis
- Arsenical
- Deficiency
- Guillain-Barré

Progressive muscular atrophy
Poliomyelitis [8]
Scleroderma
Hypopituitary cachexia (Simmonds' disease)
(No case of Werdnig-Hoffmann syndrome seen)

In one case of myotonia congenita ribose was not found, but only a dilute specimen of urine was available.

COMMENT

It seems from the results of this study that the presence of *d*-ribose in the urine, unlike creatinuria, is not simply the result of muscular wasting, since patients with more advanced wasting than those with muscular dystrophy showed no evidence of this sugar. Thus, it would appear that the presence of ribose is due to a specific error of cell metabolism, possibly not confined to the muscular dystrophies, but universally present in them. It is interesting that progressive neuropathic (peroneal) atrophy (Charcot-Marie-Tooth disease) and myasthenia gravis, which are frequently classified with the muscular dystrophies, show no ribose and therefore presumably do not belong to this group.

SUMMARY AND CONCLUSION

The method of detection and identification of ribose in the urine is described.

Patients with progressive muscular dystrophies, myotonia congenita, and amyotonia excrete in their urine complexes containing *d*-ribose.

8. Transitory presence of ribose found in some cases during the febrile stage only (unpublished data from this laboratory).

A THEORY OF FRONTAL LOBE FUNCTION

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THIS PAPER presents a simple, unifying theory of the function of the frontal lobe. The theory was developed in 1946 and first presented orally at the meeting of the American Psychiatric Association in 1949 as part of my comments on a paper by Hoch.[1] At that time the hypothesis was well received by the audience, and encouragement was given me to develop it further and to find supporting evidence, which I present here for the first time in written form.

I. THE THEORY

The theory which describes what may be called briefly the persistence function of the frontal lobes is as follows (the term "frontal lobes" is used in this paper in a limited sense to refer specifically to Brodmann areas 9, 10, and 11 and to Walker's modification of Brodmann areas 13 and 14): The frontal lobes do not have a primary function, such as the mediation of sight or hearing, but, rather, act secondarily through their connections to maintain, or sustain, emotional states, trains of association, and motor actions, or the inhibition of such actions. In performing this persistence, or sustaining, function, the frontal lobes in the most general terms add energy to, or prevent the loss of, energy from systems which without this added or conserved energy would operate at a different intensity, or rate, or would not continue to operate at all. Again, speaking generally, the type of function sustained by this frontal-lobe activity is that which ordinarily can be brought under voluntary control, but which may operate without help of the frontal lobe. The meaning of these general statements should become clearer as the paper progresses.

II. CLINICAL EVIDENCE IN SUPPORT OF THE THEORY

The development of this theory of persistence function and its verification by clinical observation resulted from my personal observations on more than 400 lobotomy patients at the Boston Psychopathic Hospital from Jan., 1946, to Jan., 1949. More than 300 of these patients were observed before and after operation. The observations made on 205 of these patients have previously been reported.[2]

From the Connecticut State Hospital and the Department of Psychiatry of Yale University School of Medicine.

1. Hoch, P.: Theoretical Aspects of Frontal Lobotomy and Similar Brain Operations. Am. J. Psychiat. **106**:448-453, 1949.

2. Arnot, R.; Talbot, B., and Greenblatt, M.: One to Four Years Follow-Up of 205 Cases of Bilateral Prefrontal Lobotomy, in Greenblatt, M.; Arnot, R., and Solomon, H. L., Studies in Lobotomy, Editors, New York, Grune & Stratton, Inc., 1950.

The evidence for the theory will include, first, these clinical observations and then the clinical observations of others; second, reports of anatomical and physiological studies from the literature, and, third, summaries of psychological studies from the literature. Finally, comparisons with other theories will be made.

The manifestations of this persistence function observed clinically in lobotomy patients may be classified under three groups: improvements in specific diagnostic groups, improvements in specific signs and symptoms, and impairments or undesirable sequelae.

The results in specific diagnostic groups following lobotomy are shown in Table 1. The diagnostic groups in which improvement occurs most consistently are those of psychoneurosis, hypochondriasis; psychoneurosis, obsessive-compulsive type; involutional psychosis, melancholia, and manic-depressive psychosis, depressed type. The involutional-melancholia group will be used to illustrate the theory of persistence function because it typifies the clinical condition that will invariably be helped by lobotomy if the diagnosis is correct and the operation adequate. This

TABLE 1.—*Improvement in Specific Diagnostic Groups Following Lobotomy**

Diagnostic Category	Good and Fair Results Following Lobotomy, %	Total No. of Patients Observed
Psychoneurosis, hypochondriasis	100	3
Psychoneurosis, obsessive-compulsive	100	7
Involutional psychosis, melancholia	92	12
Manic-depressive psychosis, depressed type	87	15
Paranoid condition, without hallucinations	75	20
Dementia praecox, other types	70	27
Organic psychosis	50	6
Dementia praecox, catatonic type	43	35
Dementia praecox, paranoid type	22	31
Manic-depressive psychosis, manic (chronic) type	20	5
Dementia praecox, hebephrenic type	12	18

* Modified from Table 7,[2] p. 194.

condition has been described elsewhere [3] as an essentially unremitting state of tortured self-concern, that is, a state characterized by worry, fear, tension, and depression, with the attention directed mainly toward the self. The term "agitated depression," when used as a substitute for the term "involutional melancholia," clearly describes the state of the patient prior to operation. After operation the patient experiences a striking alleviation of his state of misery.

My observation has been that the patient has not lost his ability to feel worried, fearful, tense, or depressed, but, rather, that he has had a reduction of his ability to persist in such a state.

Obviously, frontal lobotomy is not the only means of interrupting this persistence function of the frontal lobes and their connections. A normal person can "voluntarily" interrupt it and turn to another interest. In normal people or in only moderately pathological persons, such as those with mild obsessive-compulsive psychoneuroses, the function can be interrupted by use of alcohol or sedation. In even more pathological people, for example, those with agitated depressions, electric

3. Arnot, R.: Clinical Indications for Prefrontal Lobotomy, J. Nerv. & Ment. Dis. **109**:267-269, 1949.

shock will almost always interrupt this persistence function. Only in cases in which the pathological state is of long duration or returns repeatedly after electric shock would frontal lobotomy need to be utilized.

The conclusion is, then, that in these pathological diagnostic groups in which the disease is relieved by lobotomy this persistence function, which prior to illness would act intermittently, has come to operate almost continuously, and perhaps at an increased intensity. The improvements following lobotomy come from an interference with this function.

The second group of clinical observations in support of the theory is found in the improvements in specific signs and symptoms after lobotomy.

The sign of refusal of food (Table 2) will be taken as an example of the pathologically excessive activity of the preoperation persistence function and of the postoperative improvement when this function has been reduced. The hypothesis is that in order that this inhibitory set of refusing food may be maintained or persisted in, the frontal lobes must be intact. The observation in support of the

TABLE 2.—*Improvement in Specific Signs and Symptoms Following Lobotomy**

	Improvement Following Lobotomy, %	Total No. of Patients Observed
Refusal of food	100	35
Fear	87	65
Worry	86	118
Depression	86	66
Lack of cooperation	80	70
Destructiveness	78	27
Resistiveness	75	82
Combativeness	73	48

* Modified from Tables 1 and 2,[2] pp. 98-99.

theory is that 100% of 35 patients who refused food prior to operation did not do so afterward.

Actually, the postlobotomy patient has not lost his ability to refuse food, because he certainly can, and does, do so, but he has undergone a reduction in the ability to maintain this set long enough for it to become a problem to the nurses. Stated in other terms, he has not lost his ability to inhibit, or lost his inhibitions, as is sometimes said; rather, he has experienced a diminution in his ability to sustain the inhibition. That the patient has had this reduction, but not a complete loss, is shown not only by his still being able temporarily to refuse food but also by his ability temporarily to refrain from swearing or acting aggressively if the situation really demands such restraint of him.

Further observations in support of the theory are found in Table 2, in which it can be seen that 87% of the patients with excessive fear, 86% with excessive worry, and 86% with severe depression lost these symptoms after lobotomy. Again, these patients did not lose their ability to feel fear, worry, or depression; rather they underwent reduction in their ability to maintain the set, to sustain the emotion long enough to be considered pathological or to require help. For example, patients who before operation would remain smolderingly angry for many days, would after operation flare up into anger which lasted only 5 or 10 minutes. The emotional state was not sustained. This reduced ability to sustain a state of emotion, such

as fear, depression, or anger, or to maintain a state of inhibition, such as negativism, would explain the improvement after operation with respect to lack of cooperation (80% of cases), resistiveness (75%), and combativeness (73%).

Further manifestations of this persistence function are observed in cases of "pain." The so-called relief of pain following the operation is probably due not to a change in the sensation of the pain itself but, rather, to the reduced ability of the patient to sustain a state of worry and fear about the pain. The apparent paradox of the patient's being "relieved" of pain and yet showing what appears to be an increased reaction to pain may also be explained by stating that the marked reaction of the postlobotomy patient to the touch of the needle, or even to the sight of the needle, is due to the patient's failure to maintain the inhibition against the withdrawal response.

Finally, the improvement in symptoms of the obsessive-compulsive neurosis following lobotomy has a similar explanation. The patient still has, for example, his fear of germs, but his ability to sustain the often paralyzing state of intense apprehension and worry is diminished.

TABLE 3.—*Development of Undesirable Sequelae Following Lobotomy**

	Patients Exhibiting the Sequela, %	Total No. of Patients Observed
Excessive appetite	51	128
Outspokenness	47	66
Lack of initiative	42	52

* Modified from Tables 1 and 2,[3] pp. 98-99.

The third group of clinical observations which supports the theory of the persistence function of the frontal lobes are the postlobotomy sequelae (Table 3). These sequelae are, as Cobb [4] has remarked, really the obverse of the pathological symptoms that are improved by lobotomy; for example, the patient who refuses food before operation takes an excessive amount after operation. The explanation of the increased intake of food would be that the patient has difficulty in sustaining the state of inhibition against his hunger impulses until the next meal and in many cases tends to eat almost whenever he sees food, a symptom which accounts for the large gain in weight frequently observed in postlobotomy patients.

The development of the sign of outspokenness also appears to be due to a difficulty in maintaining the state of inhibition against the hostile or improper word that before lobotomy would not be spoken, but which after lobotomy is expressed. Here, too, however, if the situation is extremely important to the patient, he may continue, at least temporarily, to sustain the inhibition and not speak the word. To repeat, he has not "lost his inhibitions"; rather, he has experienced a reduction in his ability to sustain the inhibitions.

Another common sequela of lobotomy, lack of initiative, has a possible twofold explanation according to the persistence theory. On the one hand, the patient does not maintain the facilitative set for staying at work; on the other, he does not

4. Cobb, S.: Function of the Frontal Areas of the Human Brain, in Borderlands of Psychiatry, Cambridge, Mass., Harvard University Press, 1943.

sustain the inhibitive set against reacting to distracting stimuli. He, therefore, is often a poor worker, particularly in the first months after the operation, and is described as lazy.

The chimpanzees Lucy and Becky, described by Fulton and Jacobsen,[5] showed a similar change in that they did not stay at their food-seeking task well enough to become frustrated. They, too, presumably, failed to sustain a facilitative set for working on the problem and an inhibitive set against reacting to distracting stimuli.

The clinical observations cited here as evidence for the theory are essentially the same as those reported by other observers—the Connecticut Lobotomy Committee,[6] Freeman and Watts,[7] and Partridge.[8]

Moreover, a clinical observation made 74 years, before the first modern therapeutic lobotomy, also supports the theory. Harlow[9] reported the case of Phineas Gage, who suffered, as Cobb[4] believes, damage to Areas 8, 9, 10, and 11, when a dynamite explosion drove a crowbar into his skull. Dr. Harlow wrote of his patient: "Previous to his injury, though untrained in the schools, he possessed a well-balanced mind, and was looked upon by those who knew him as a shrewd, smart business man, very energetic and persistent in executing all his plans of operation." After the injury and the subsequent recovery, he was reported as "capricious and vacillating, devising many plans of future operation which are no sooner arranged than they are abandoned for others appearing more feasible."

If agreement is reached that the theory of the persistence function of the frontal areas explains the clinical observations, the next problem is to determine whether the theory is in accord with established anatomical and physiological knowledge of the frontal lobes.

III. ANATOMICAL AND PHYSIOLOGICAL KNOWLEDGE OF THE FRONTAL LOBES

In a review of the literature on the anatomical and physiological knowledge of the frontal lobes, no evidence was found that would contradict the persistence theory. In fact, certain studies were found that aid in understanding how such a function might be mediated.

Jackson[10] wrote: "I have long held the hypothesis that the whole of the anterior lobe is (chiefly) motor."

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5. Fulton, J. E., and Jacobsen, C. F.: Functions of the Frontal Lobes: A Comparative Study in Monkeys and Man, Proceedings Second International Neurological Congress, London, 1935, pp. 70-71.

6. Connecticut Lobotomy Committee (Friedman, S.; Moore, B. E.; Simon, B., and Farmer, J.): A Co-Operative Clinical Study of Lobotomy, A. Res. Nerv. & Ment. Dis., Proc. **27**:769-794, 1948.

7. Freeman, W., and Watts, J. W.: Frontal Lobe Functions as Revealed by Psychosurgery, Digest Neurol. & Psychiat., Inst. of Living **16**:62-68, 1948.

8. Partridge, M.: Pre-Frontal Leucotomy, Oxford, England, Basil Blackwell & Mott, Ltd., 1950.

9. Harlow, J. M.: Recovery from the Passage of an Iron Rod Through the Head, Pub. Mass. M. Soc. **2**:338-340, 1868.

10. Jackson, J. H.: Selected Writings of John Hughlings Jackson, edited by James Taylor and others, London, Hodder & Stoughton, Ltd., 1921-1932.

Von Economo [11] described the areas for the simplest motilities as being in the precentral gyrus and stated that the motilities increased in complexity toward the frontal pole.

Freeman and Watts,[12] as well as Fulton,[13] stated the same principle more specifically by saying that crude motor movements are mediated through Area 4 and more skilled motor movements through Area 6. They left open the possibility that the more anterior areas may also have a motor function of the sustaining type described in this paper.

Bailey [14] confirmed this view in his report on cytoarchitectural studies and electrical-stimulation experiments on the frontal lobes of man and chimpanzees.

> . . . As we move forward over the surface of the hemisphere anterior to the central sulcus the movements become grosser and increasingly difficult to elicit, as the Betz cells disappear and the cortex becomes granular, so that finally only tardy, slow and persistent movements can be obtained of the head and eyes.

Although the present paper is intended primarily to explain *what* the persistence function is, rather than to explain *how* the function is mediated, the above citations suggest that this persistence function could be a special type of motor activity. At least, they indicate that a persistence function of the type here described is in keeping with the known anatomical and physiological knowledge of the frontal lobes.

IV. PSYCHOLOGICAL STUDIES OF FRONTAL-LOBE FUNCTION

At present, psychological studies are being conducted in the Connecticut State Hospital to test the persistence theory; but although the results confirm the findings of other investigations, summarized here, these tests have not yet been performed on enough patients to justify our reporting the results. For psychological evidence in support of the theory we shall have to depend, therefore, on the reports of others.

Most psychological investigators report that surprisingly little change is found after lobotomy when routine tests, such as the Bellevue-Wechsler, Rorschach, and Shipley-Hartford tests, are used. In order to detect the changes produced by lobotomy, special tests have to be utilized, tests which, we believe, actually evaluate changes in the persistence function of the frontal lobes.

Yacorzynski and associates [15] studied one patient thoroughly for level of aspiration and degree of effort. They found that the patient "showed a consistently high level of aspiration before and after operation. In working towards a goal, however, he tended to use the less difficult methods [page 647]."

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11. von Economo, C.: Cytoarchitectonics of the Human Cerebral Cortex, translated by S. Parker, London, Oxford University Press, 1929.

12. Freeman, W., and Watts, J. W.: Psychosurgery, Springfield, Ill., Charles C Thomas, Publisher, 1942.

13. Fulton, J. F.: Functional Localization in Relation to Frontal Lobotomy, London, Oxford University Press, 1949.

14. Bailey, P.: Concerning Cytoarchitecture of the Frontal Lobes of Chimpanzee (Pan Satyrus) and Man (Homo Sapiens), A. Res. Nerv. & Ment. Dis., Proc. **27**:84-94, 1948.

15. Yacorzynski, G.; Bosher, B., and Davis, L.: Psychological Changes Produced by Frontal Lobotomy, A. Res. Nerv. & Mental Dis., Proc. **27**:642-657, 1948.

Rylander,[16] who, incidentally, reported that the intelligence quotient was regularly lowered, at least minimally, in neurotic patients after operation, made an observation on what can be interpreted as the persistence function (page 697).

> . . . A rather striking change was revealed in the word enumeration test. A subject must name as many nouns as possible during three minutes with eyes closed to exclude visual stimulation. A definite and considerable reduction followed the operation. Patients start enumerating the words, then suddenly stop, complaining, "My brain becomes blank. I run completely out of words. I can't think any more."

Rylander [16] noted further, as did Goldstein,[17] that the power of abstraction was reduced. This difficulty in abstraction, he believed, is similar to the running out of words in the above test: "The defects in abstract thinking probably have their background in the reduced association power [page 701]."

Robinson [18] made many observations in support of the persistence theory. In fact, she developed a similar theory which differs only in that it is restricted to a specific application of the broader theory offered in the present paper. After many clinical observations, she theorized that "prolonged attention" was the function interfered with by lobotomy (page 427):

> It seemed to the writer that prefrontal lobotomy must inevitably lessen this capacity for attention, this capacity (at once facilitative and inhibitive) for maintaining and prolonging an idea against distraction.

Furthermore, she hypothesized that this prolonged attention would appear in cognitive activities as a capacity for deliberation, and in motor activities as a capacity for behaving deliberately.

In order to evaluate her hypothesis, Robinson found that some of the best tests for prolonged attention were those devised by Downey,[19] one of which may be cited here. The subject is asked to write "United States of America" as slowly as possible. Robinson reported (page 431):

> . . . It was interesting to watch the lobotomy patients at work at this task. They seemed, as always, to be making an effort to do as they were asked, but their hands would move slowly for a few seconds only and then would resume normal speed. Apparently they *could not* slow themselves down.

This observation, I believe, could be interpreted as indicating that the set of partial inhibition required by the test could not be sustained.

In her summary, Robinson stated that lobotomy patients do not show any "unique" changes in the Rorschach or the Binet tests, nor do they show deficiencies in the Shipley-Hartford test for abstract thinking or in the Hunt-Minnesota test for learning. On the other hand, "They do significantly less well than the controls on tests demanding deliberative behavior (Downey's Speed of Decision, Volitional

16. Rylander, G.: Personality Analysis Before and After Lobotomy. A. Res. Nerv. & Ment. Dis., Proc. **27**:691-705, 1948.

17. Goldstein, K.: Significance of the Frontal Lobes for Mental Performances, J. Neurol. & Psychopath. **17**:27-40, 1936-1937.

18. Robinson, M. F.: What Price Lobotomy? J. Abnorm. & Social Psychol. **41**:421-434, 1946.

19. Downey, J. E.: The Will Temperament and Its Testing, Yonkers, N. Y., World Book Company, 1923.

Perseveration, and Motor Inhibition)." She concluded from her observations, therefore, that her theory is confirmed and that lobotomy "reduces the capacity for prolonged attention." Or, as I should theorize more inclusively, the persistence function of the frontal lobes and their connections is interfered with.

V. COMPARISON WITH OTHER THEORIES

Many theories of frontal-lobe function have been developed on the basis of clinical observation of patients with injury or operative damage to the frontal lobes. Lobotomy has, however, presented the largest number of cases and the principal opportunity for the development of hypotheses. A careful review of the other theories leads to the conclusion that many of them are specific applications of the broader persistence theory presented in this paper, as will be seen from a consideration of the following examples.

Goldstein [17] concluded that the frontal lobes were necessary for a person to be able to maintain the power of abstraction. That the power of abstraction is dependent on the persistence function has already been indicated in the discussion of Rylander's observations.

Brickner [20] developed a theory that his lobotomized patient could not synthesize simple engrams into complex patterns. Again, this inability may be interpreted as a defect in the persistence function.

Freeman and Watts [12] have proposed several theories which appear to be applications of the present theory. They stated (page 313):

> It is the capacity of foresight in relation to himself that is particularly lacking [in a postlobotomy patient]. It might well be that if the individual stopped to think, counted ten before he struck, the result would be different.

There is in such a patient, apparently, a failure to maintain the inhibition against the socially undesirable act. Further, the patient apparently fails to sustain the chain of thought or state of reverie sufficiently really to picture the future situation that may follow from his act.

Freeman and Watts [7] also concluded that "creative artistry is impossible for a patient who has had a lobotomy." Again, this conclusion can be explained theoretically by postulating the reduction of persistence function, for certainly the highest type of creative effort requires, in most instances, a sustained, frequently grueling, effort. In the art-therapy classes at the Connecticut State Hospital, it has repeatedly been observed that postlobotomy patients require frequent urging from the therapist to finish their work.

The preceding theories, as well as the persistence theory, are really hypotheses about *what* the frontal lobes do, and, except for the suggestion that this persistence may be a motor function, I have avoided the problem of *how* the frontal lobes carry out this function and of how the lobotomy effects the changes. There are, however, two theories, those of "morbid constellations" and of "long circuiting," that are combinations of *what* the frontal areas do and *how* they do it.

20. Brickner, R. M.: The Intellectual Functions of the Frontal Lobes, New York, The Macmillan Company, 1936.

Egas Moniz [21] believed that before lobotomy the pathological ideas dominated the patient's mind because there were "morbid constellations" of cells, which had to be disrupted for the benefits to be achieved.

Freeman answered the question of how the effects following lobotomy were achieved by saying that "long circuiting" had been interfered with. Cobb [22] had previously described this mechanism as a function of cortical association areas, and added (page 65):

> . . . The more destroyed, the less "long circuiting" remains. No specific trait or character of man is taken away. The essential point is that the extraordinarily extensive mechanism for association has been reduced.

The conclusion drawn from this review of previous theories of frontal-lobe function is that many of them are specific applications of the present, broader persistence theory, for which they also directly and by implication appear to offer further support.

SUMMARY

A theory of the function of the frontal lobes is offered which states that a function of the frontal lobes and their connections is to aid the persistence of emotional states, chains of thought, motor actions, and motor inhibitions.

Support for the theory is found in clinical observation of patients before and after frontal lobotomy. States of worry, fear, depression, tension, and negativism are relieved, while conditions of excessive intake of food, outspokenness, and lack of initiative are developed. Both the benefits and the deficits following lobotomy are considered to be evidences of the reduction of this persistence function.

Anatomical and physiological knowledge of the frontal lobes and their connections offers no contradiction to the present theory.

Psychological studies, indirectly and directly, offer support for the persistence theory. On the one hand, they show that the frontal lobes do not have a function that can be measured by the routine psychological tests, which mostly show no significant changes after operation. On the other hand, they show that the studies which do delineate changes after lobotomy are those that measure manifestations of this persistence function—for example, the tests for a decrease in prolonged attention used by Robinson.

A review of other theories of frontal-lobe function indicates that some of them are specific applications of this broader persistence theory.

21. Egas Moniz: Tentatives operatoires dans le traitement de certaines psychoses, Paris, Masson & Cie, 1936.

22. Cobb, S.: A Preface to Nervous Disease, Baltimore, William Wood & Company, 1936.

CEREBRAL ANGIOGRAPHY WITH IODOPYRACET INJECTION U.S.P. (DIODRAST®)

Its Dangers, Particularly in Hydrocephalic Infants

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AND
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CEREBRAL angiography has proved invaluable in the diagnosis of certain cerebral lesions. The increasing number of patients subjected to this procedure necessitates an awareness of its hazards.

Gross,[1] in 1940, first used iodopyracet (diodrast®; the diethanolamine salt of 3,5-diiodo-4-pyridone-N-acetic acid) for cerebral angiography in this country. He reported no alterations in the brains of dogs subjected to angiography with 35%, 50%, and 70% solutions of this medium. Convulsive seizures, however, occurred in 3 of 10 human subjects in whom he used a 70% solution. Gross recommended the use of a 50% solution, which he believed safe. He reported inadequate visualization with the 35% solution. Kristiansen and Cammermeyer [2] found no abnormality in the brains of 13 rabbits that had received 17 injections of 35% iodopyracet.

Broman and Olsson,[3] however, showed that contrast media of the iodopyracet type "are capable of causing a damage solely of the BBB (blood-brain barrier), the demonstration of which requires the application of a special technique." They used trypan blue, to which the cerebral vessels are normally impermeable. If the vascular permeability is impaired, however, the trypan blue will escape into and stain the surrounding tissue. Using rabbits, cats, and guinea pigs, they showed that the iodopyracet compounds in concentrations of 35 to 70% altered the permeability of the cerebral blood vessels. In the cases [4] in which the injury was rather severe edema and punctate hemorrhages occurred.[5]

From the Department of Neurosurgery, New York Medical College and the Neurosurgical Service of the Jewish Hospital of Brooklyn.

1. Gross, S. W.: Cerebral Arteriography by Means of a Rapidly Excreted Organic Iodide, Arch. Neurol. & Psychiat. **44**:217-222 (July) 1940.

2. Kristiansen, D., and Cammermeyer, J.: Experimental Investigation of the Effect of Arteriography with Perabrodil on the Brain, Acta radiol. **23**:113-130, 1942.

3. Broman, T., and Olsson, O.: The Tolerance of Cerebral Blood Vessels to a Contrast Medium of the Diodrast Group, Acta radiol. **30**:326-342, 1948.

4. Broman, T., and Olsson, O.: Experimental Study of Contrast Media for Cerebral Angiography with Reference to Possible Injurious Effects on Cerebral Blood Vessels, Acta radiol. **31**:321-334, 1949.

5. Bloor, Wrenn, and Hayes (Bloor, B. M.; Wrenn, F. R., Jr., and Hayes, G. J.: J. Neurosurg. **8**:435-440 [July] 1951) have published the results of their interesting experiments since this report was prepared. These authors used a combined method of indicator-dye injection and electroencephalography to demonstrate functional and structural changes in rabbits after cerebral angiography with iodopyracet injection.

Neurosurgeons now widely use iodopyracet, usually in a 35% solution. Although hemiplegia, at times permanent, occasionally follows this test, there have been no pathologic studies to clarify its mechanism. Engeset [6] reported two deaths in a series of 100 cases in which he used a 35% solution of iodopyracet for cerebral angiography, but he did not attribute the fatalities to the angiographic procedure. He cited Lohr as having had one fatality in a hemophiliac and two in hypertensive patients. Lohr did not make pathologic studies. In fact, we know of no record of pathologic study any patient who died of the effects of cerebral angiography.

Chusid, Robinson, and Margules Lavergne [7] recorded two cases of transient hemiplegia after angiographic studies with a 35% solution of iodopyracet. Their report was made before the New York Society of Neurosurgery, and "in the general discussion 21 similar complications following cerebral angiography with 35 per cent Diodrast were reported."

In a series of 330 cerebral angiograms made on 277 patients, Olsson [8] recorded 3 cerebral complications in adults. The diagnoses in these cases were cerebral thrombosis, oculomotor-nerve paralysis of undetermined origin, and astrocytoma of the temporal lobe. The respective complications in these cases were left hemiparesis, mental confusion of one day's duration, and accentuation of left hemiparesis. The carotid artery was punctured percutaneously in these three cases.

In a series of 96 patients (in 92 of whom the carotid artery was successfully punctured percutaneously), Culbreth, Walker, and Curry [9] found that "transient hemiparesis and/or aphasia has been seen in 4 patients. In only 1 case of suspected cerebral thrombosis could the procedure have been contributory to the patient's demise."

Wise, Hughes, and Hannan [10] recorded 1 death in a series of 150 arteriographic tests. The death was that of a man aged 54, who suddenly ceased breathing four hours after the arteriographic procedure. "The cause of death, however, was not clear, and autopsy findings were inconclusive. Another patient experienced mental confusion associated with a positive Babinski sign, which cleared spontaneously in thirty-six hours. A seventeen year old girl developed jacksonian convulsions which cleared in thirty-six hours."

Dunsmore, Scoville, and Whitcomb [11] reported 14 complications of cerebral angiography with a 35% solution of iodopyracet in a series of 147 angiographic studies on 198 adult patients. These included "3 fatalities, 4 cases of transitory hemiplegia, 2 cases of convulsions, 1 case of carotid artery thrombosis, 1 case of injury to the cervical sympathetic chain, and 1 case of Diodrast skin sensitivity." In the first of their fatal cases, "it was the feeling that the extravasation of blood

6. Engeset, A.: Angiography with Diodrast, Acta radiol. (Supp.) **56**:1, 1944.

7. Chusid, J.; Robinson, F., and Margules Lavergne, M.: Transient Hemiplegia Associated with Cerebral Angiography (Diodrast), J. Neurosurg. **6**:466-474, 1949.

8. Olsson, O.: Cerebral Angiography: Tolerance for Contrast Media of Diodrast Type, J. Neurol., Neurosurg. & Psychiat. **12**:312-316, 1949.

9. Culbreth, G.; Walker, A. E., and Curry, R.: Cerebral Angiography in "Brain Tumor Suspects," J. Neurosurg. **7**:127-138, 1950.

10. Wise, R.; Hughes, R., and Hannan, J.: Cerebral Arteriography, Am. J. Roentgenol. **64**:239-254, 1950.

11. Dunsmore, R.; Scoville, W., and Whitcomb, B.: Complications of Angiography, J. Neurosurg. **8**:110-118, 1951.

into the neck had caused bilateral jugular compression and secondary venous stasis in the brain and that this, in turn, led to edema and respiratory failure of central origin." They found cerebral infarctions in the other two fatal cases but did not record detailed studies of the brain with particular reference to changes in the carotid and cerebral arteries.

Uihlein [12] reported several complications in a series of 100 angiographic studies on 77 patients from the Mayo Clinic. Three patients had transient hemiplegia or hemiparesthesia, and one had nominal aphasia, persisting three months after the angiographic procedure. No mention is made of the type of angiography used in the cases in which complications developed, but the percutaneous method was used in 85% of their total cases. "One elderly patient died two days after angiography, of thrombosis of the middle cerebral artery. Thrombosis was suspected clinically prior to angiography." Uihlein, therefore, believed that the fatality was not directly attributable to the immediate effects of angiography. Autopsy studies in this case were not recorded.

We know of no record of serious sequelae from iodopyracet angiography in children. We feel obliged, therefore, to report our clinical and pathologic observations on three hydrocephalic children who died after cerebral angiographic studies with iodopyracet. We also mention serious complications which we have experienced in adults. These studies throw light on a mechanism that produces complications in the use of this diagnostic technique in patients of any age.

Case 1.—M. W., a girl aged 2½ years, entered the hospital because of pain in the legs and staggering. Birth and early development had been normal. Although the child started walking at the age of 13 months, she was said to have fallen frequently. This difficulty became more pronounced one month before admission, when she began to complain of pain in the legs. Headache and vomiting occurred. The abnormal findings on neurologic examination were (1) papilledema of 6 D. in the right eye and pallor of the left optic disk, which was rather sharply outlined; (2) inequality of the pupils, the left being somewhat larger than the right (sluggish reaction of the left pupil to light, with fixation of the left), and (3) somewhat unsteady gait.

A tumor of the left subfrontal region was suspected, chiefly because of the optic nerve atrophy on one side and the papilledema on the other. The electroencephalogram was normal. Roentgenograms of the skull showed wide separation of the coronal, sagittal, and lambdoid sutures. An angiogram of the left internal carotid artery was made by the open method on Dec. 4, 1950. Two injections, each of 15 cc. of 35% iodopyracet solution, were made for anteroposterior and lateral views. There was no angiographic abnormality. When the child awoke from anesthesia, she showed right spastic hemiparesis and paralysis of right lateral conjugate deviation of the eyes. This persisted throughout the patient's hospital course.

On Dec. 12, ventriculographic study revealed marked hydrocephalus, involving both lateral ventricles and the third ventricle. The fourth ventricle was not seen. Semicoma followed this procedure, and a suboccipital craniectomy was immediately done. A large medulloblastoma, involving the left cerebellar hemisphere and the bermis, was found and partially removed. An hour later, respiratory difficulty, attributed to tracheal obstruction, appeared. The patient died as a tracheotomy was about to be performed.

At autopsy the brain was found to be large, weighing 1,515 gm. The left cerebral hemisphere showed a soft gray necrotic area, beginning at a point 2 cm. anterior to the occipital pole and extending forward, just above the ventricle, to the midfrontal region. The left cerebellar hemisphere was enlarged and firm. Its ventral surface showed the surgical wound. A rather circumscribed grayish-brown tumor, with a yellowish center, occupied the left cerebellar hemisphere. This mass measured 3 cm. in diameter and extended into the vermis. Coronal sections

12. Uihlein, A.: Cerebral Angiography, Proc. Staff Meet., Mayo Clin. **26**:133-139, 1951.

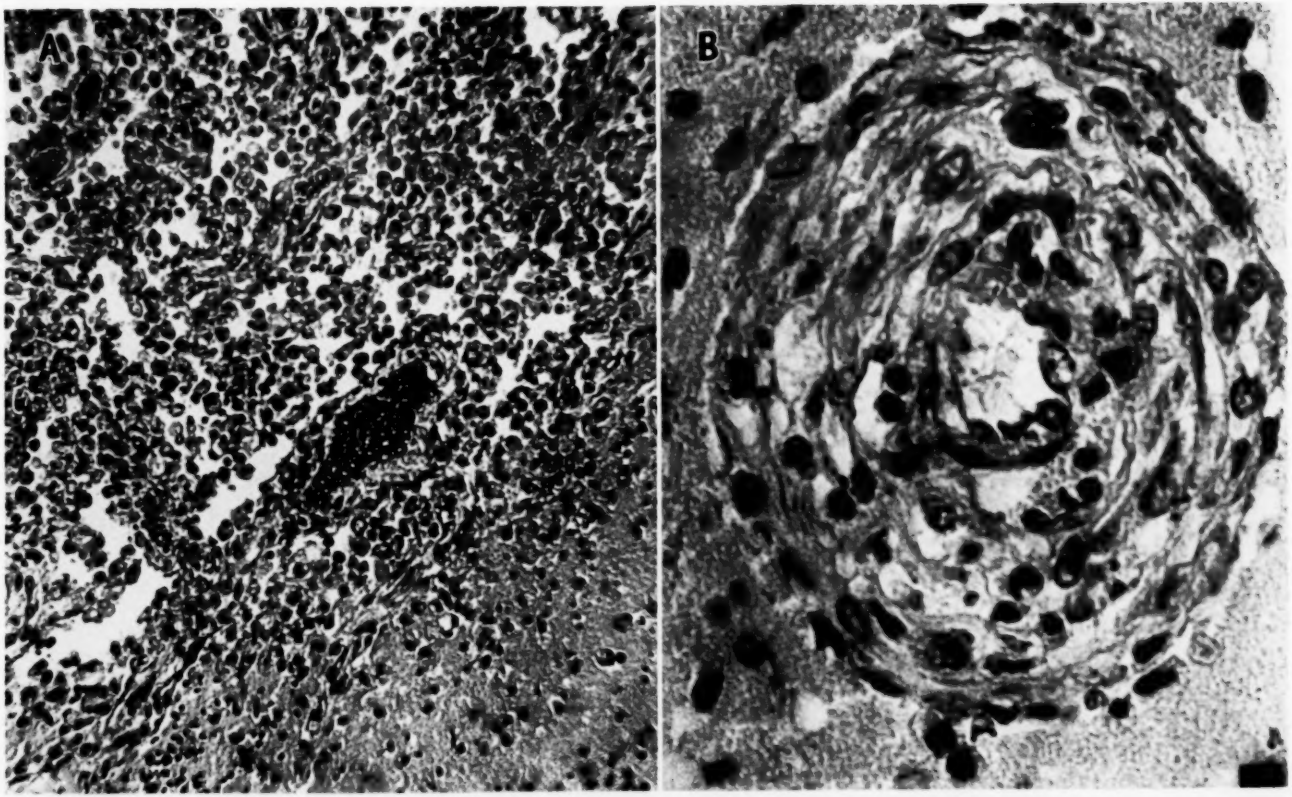

Fig. 1.—Photomicrographs showing (*A*) encephalomalacia of left cerebral hemisphere (× 350); *B*, marked endothelial proliferation of an intracerebral arteriole, left cerebral hemisphere (× 450). Hematoxylin-eosin stain.

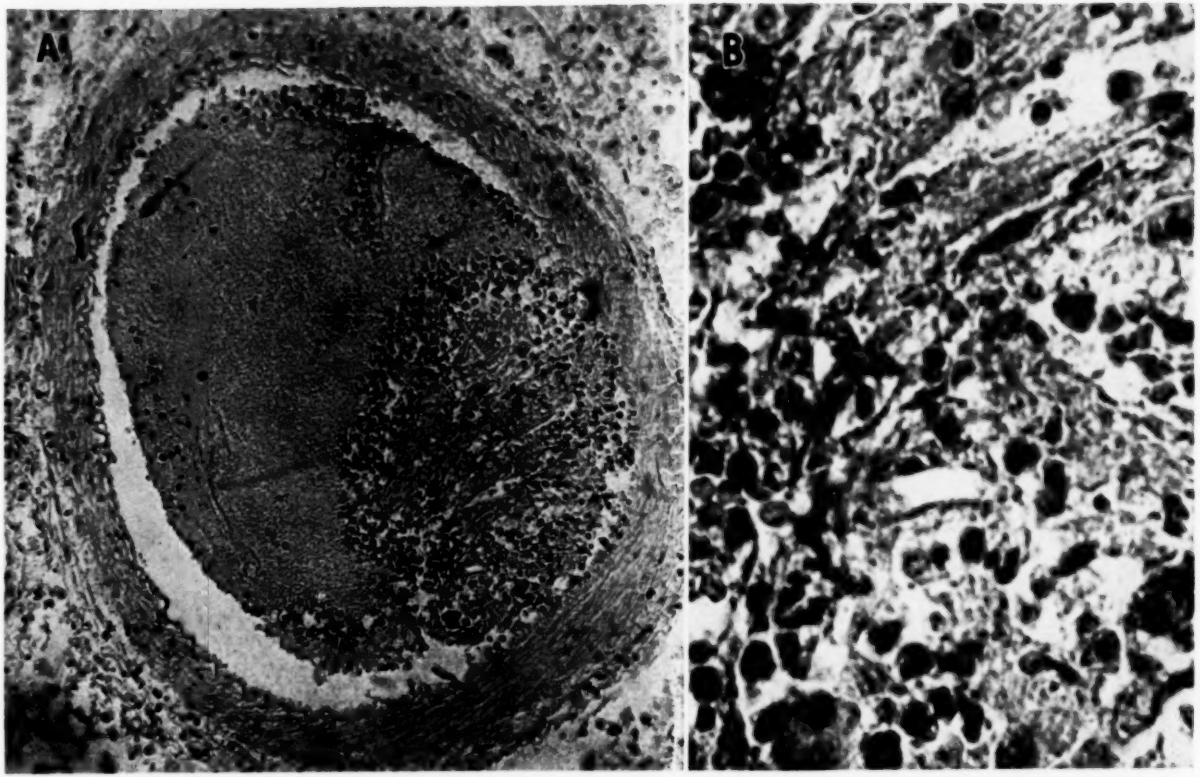

Fig. 2.—*A*, photomicrograph of a thrombosed intracerebral artery (× 20), with recanalization shown in *B* (× 400). Hematoxylin-eosin stain.

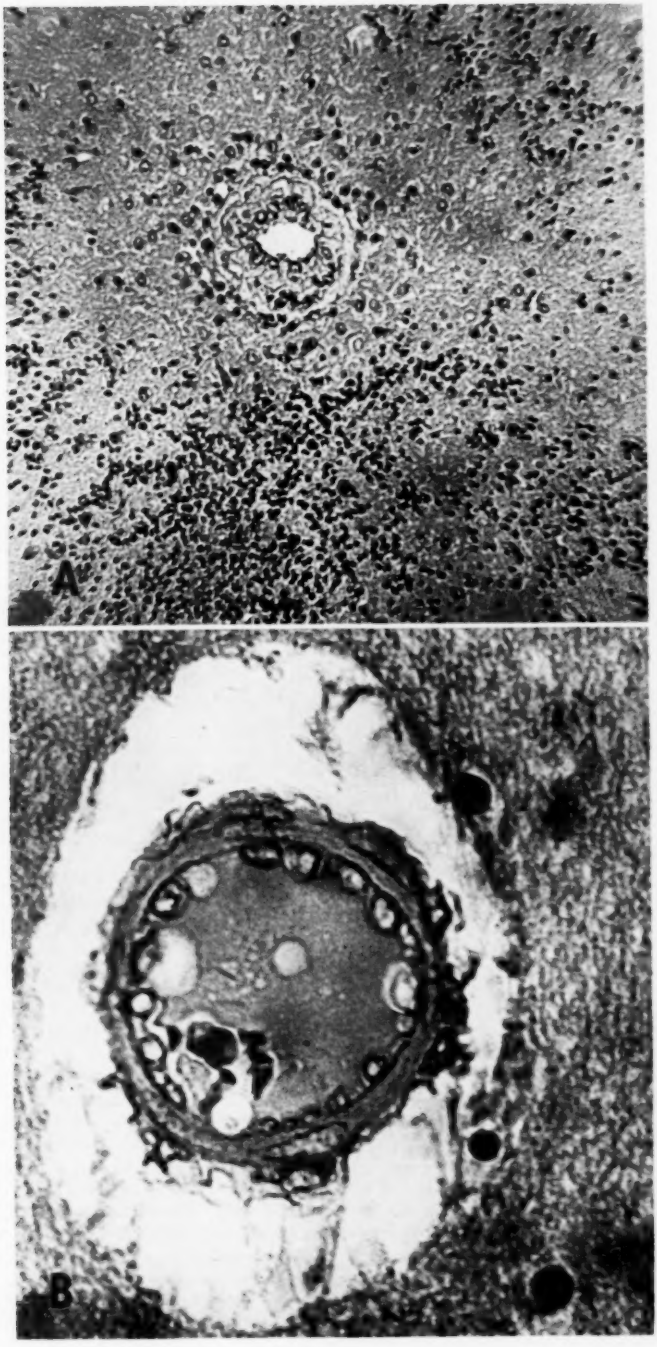

Fig. 3.—Photomicrographs showing (*A*, Case 1) endothelial swelling and extravasation of red blood cells (× 300); (*B*, Case 2) endothelial swelling of an intracerebral arteriole (× 400). Hematoxylin-eosin stains.

of the brain showed that the necrotic area in the left cerebral hemisphere was 3 cm. in depth, involving both gray and white matter. In some areas it extended from cortex to ependyma.

The large softened area in the cerebrum showed complete disorganization of structure of the gray and white matter. Abundant compound granular corpuscles were present (Fig. 1*A*). Large microglial and rod cells and hypertrophied astrocytes with fragmented processes were present in the borderline areas between the softened and the nearly normal brain. Nerve cells showed central chromatolysis and shrinkage in the border zone, and occasionally elsewhere, in both the left and the right cerebral hemisphere. More advanced degenerative forms of nerve cells were present close to the softened zone.

There was a striking change in the blood vessels. The endothelial cells were greatly swollen and hyperplastic (Fig. 1*B*). Frequently this change resulted in narrowing of the lumen and complete occlusion. In one area a thrombus was present in a medium-sized artery, which showed early recanalization (Fig. 2). These vascular changes were most prominent in and near the softened area. Endothelial swelling of capillaries was present, however, elsewhere in the left cerebral hemisphere. An occasional capillary in the brain stem showed minimal swelling of its endothelium. A few perivascular collars of lymphocytes were present near the softened

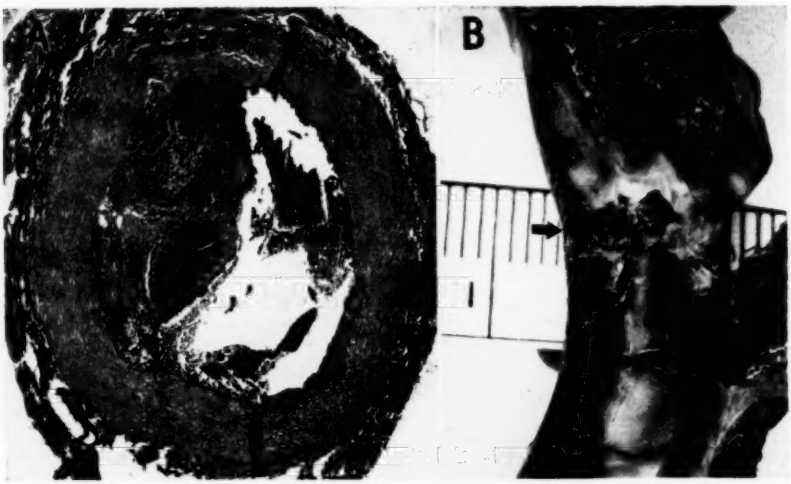

Fig. 4.—*A*, (Case 2), photomicrograph showing thrombus of the right common carotid artery at site of needle puncture; *B*, photograph showing elevated intimal plaque (arrow) at point of needle puncture of right internal carotid artery.

area, where capillary hemorrhages also occurred (Fig. 3*A*). A few lymphocytes, mononuclear cells, and polymorphonuclear cells were present in the meninges.

The tumor consisted of closely packed cells containing very little cytoplasm. The nuclei were small and round, with a dense chromatin network. The cells were frequently arranged in rows of rosettes, and there were rather large areas of necrosis. Mitotic figures were moderately abundant. The microscopic appearance of the tumor was characteristic of a medulloblastoma.

CASE 2.—F. S., a boy aged 22 months, was admitted to the hospital because of convulsions, enlarged head, and mental retardation. Birth had been normal. One week after birth the infant had convulsive movements, involving chiefly the right side. These ceased after a few days but recurred two months later. During the attacks the infant would give a sharp cry and become blue. His head and eyes would turn upward and to the right, and all extremities underwent clonic movements. These attacks were accompanied by frothing at the mouth. The infant was first admitted to the hospital at the age of 5 months. At that time a pneumenocephalogram showed some enlargement of the ventricular system.

He was discharged to the outpatient neurosurgical clinic. The circumference of the head increased from 41 cm., at the age of 5 months, to 51 cm., at the age of 1 year. The seizures continued. Mental retardation worsened. The child still could not hold up his head and did not seem to see.

He was readmitted to the hospital for possible choroid plexectomy, but complete study revealed no sign of increased intracranial pressure. In the hospital, the anterior fontanelle became soft and depressed. A pneumoencephalogram showed enlargement of the ventricular system and subarachnoid spaces. The cerebral cortex was about 1 cm. thick. A diagnosis of arrested hydrocephalus and cerebral atrophy was established.

After further observation, he was readmitted, at the age of 22 months, for a cervical carotid artery-jugular vein anastomosis, to which the parents, aware of the hopeless prognosis, agreed. At this time daily convulsions were only partially controlled by phenobarbital, ¼ grain (0.016 gm.) three times a day. The child still could not hold up his head, and blindness was definite. All extremities showed increased tonus, with hyperactive reflexes.

On Feb. 1, 1950, with the use of general endotracheal anesthesia, the common carotid arteries were exposed. One injection of 10 cc. of a 35% solution of iodopyracet was given on each side. When the needle was removed from the left side, the opening would not close spontaneously, and a fine purse-string suture was required for hemostasis. A moderate amount of blood was lost, but was replaced with 200 cc. of blood, given intravenously. The child appeared pale and fatigued after operation. On the following day dyspnea appeared, and bubbling rales were heard over the chest. The course was rapidly downhill, and the child died on Feb. 3, death occurring 38 hours after angiography.

At autopsy the brain weighed 1,120 gm. A fragile thrombus was found in the right common carotid artery (Fig. 4*A*). The entire ventricular system was much enlarged. Fatty changes had taken place in the liver, which was greatly swollen. There were also hemorrhage, edema, and atelectasis of the lungs.

Microscopically, the brain showed pronounced edema of the gray and white matter and distended perivascular and pericellular spaces. There were some rod cells and compound granular cells. Many nerve cells of the cerebrum showed moderate chromatolysis, and there were but few perivascular collars of lymphocytes. There were small extravasations of red blood cells in both cerebral hemispheres. Many of the small vessels throughout the cerebrum showed definitely narrowed lumina, resulting from the swelling (Fig. 3*B*) and proliferation of their endothelial cells.

COMMENT

The right spastic hemiparesis in Case 1 developed within a few hours after angiography and persisted up to the time of craniotomy. Pathologic study showed acute encephalomalacia, pronounced swelling and proliferation of endothelial cells, occlusion of blood vessels, and actual thrombus formation. There can be no doubt that the clinical and pathologic changes resulted from the angiographic procedure.

In Case 2 the relation of angiography to death is less clear. The patient's course was rapidly downhill after angiography, and he died within 38 hours; but, in addition to the cerebral changes, marked pulmonary and hepatic damage was observed. Hence, the patient's death cannot safely be attributed to the cerebral angiography and its effect on the brain. Undoubtedly the visceral changes were contributing, if not decisive, factors. It is problematical whether the hepatic changes resulted from the iodopyracet injection. The pathologic changes in the cerebral blood vessels and paranchyma were not as striking as in Case 1. Nevertheless, the changes in the endothelium, confined mainly to the smaller vessels in this case, were impressive. Although a thrombus was encountered in the carotid artery at the site of the puncture for the arteriogram, there was no evidence of cerebral embolism or of intracranial extension of the thrombus.

It may be argued that there was a direct relation between the basic neurologic condition in each case and the pathologic changes. Although vascular changes sometimes occur adjacent to tumors, it is most unlikely that the infratentorial tumor in Case 1 could have caused the cerebral vascular changes. Hydrocephalus was present in both cases. Endothelial swelling and proliferation, however, do not occur ordinarily in hydrocephalus. The cerebral changes appear to be directly related to the iodopyracet injections, especially in Case 1.

Iodopyracet appears to exert a damaging effect directly on capillary endothelium. The endothelial swelling and proliferation observed in our two cases of hydrocephalus support this view, as do the petechial hemorrhages of the face and neck in two of Uihlein's [12] cases. After angiography these lesions "disappeared in a few days." Uihlein's interesting clinical experience and the endothelial swelling and perivascular hemorrhages observed in our cases of hydrocephalus are the counterparts of Broman and Olsson's [13] observations on the experimental animal. These investigators recorded such changes after injection of iodopyracet compounds. The absence of organic changes in a third case of hydrocephalus [14] is not surprising (Fig. 5), since Broman and Olsson have shown that the initial injurious effect of iodopyracet is on the permeability of the cerebral blood vessels. It is probable that insufficient time elapsed for organic changes to appear in this case.

In our cases the main deleterious effect of the iodopyracet appeared to be on the vascular system, rather than directly on the nervous tissue. The latter changes are explainable as secondary effects of the former. Spasm of the carotid artery during injection of iodopyracet has been observed directly at operation from time to time. Such a reaction, a manifestation of the irritative or vasoconstrictor effect of the medium on blood vessels, might account for transitory hemiplegias observed during and after cerebral angiography, although changes in vascular permeability,[13] producing reversible effects, may also be the explanation.

The presence of a thrombus in the carotid artery at the site of the needle puncture in Case 2 is of special interest in relation to certain complications of cerebral angiography. We have had another case of thrombosis of the carotid artery at the site of the needle puncture (Fig. 4*B*), that of a man aged 55 with arteriosclerosis, who exhibited progressive memory loss, ataxia, and convulsive seizures. Pneumencephalograms showed evidence of cerebral atrophy. Giving in to the insistence of the man's wife, who was grasping at straws in an attempt to relieve her husband of his incapacitating illness one of us (I. M. T.) and colleagues [15] decided to perform the then newly introduced operation of Beck, McKhann, and Belnap. This operation consists of anastomosing the distal stump of the internal jugular vein with the common or the external carotid artery. Its

13. Broman and Olsson, footnotes 3 and 4.

14. After completion of this report, we had a third case, that of a 17-month-old infant with arrested hydrocephalus, who died suddenly three hours after cerebral angiography. Four injections, each of 8 cc. of a 35% solution of iodopyracet, were made. Autopsy revealed a thrombus in the left common carotid artery at the site of the injection (Fig. 5). The thrombus was firmly attached to the vessel wall. Examination of the brain showed agenesis of the corpus callosum. No microscopic abnormalities beside the thrombus were observed.

15. Tarlov, I. M.; Shuer, B.; Epstein, B.; Hirsch, E., and Nissen, R.: Brain Revascularization After Carotid-Jugular Anastomosis Assessed by Angiography, Arch. Neurol. & Psychiat. **64**:847-860 (Dec.) 1950.

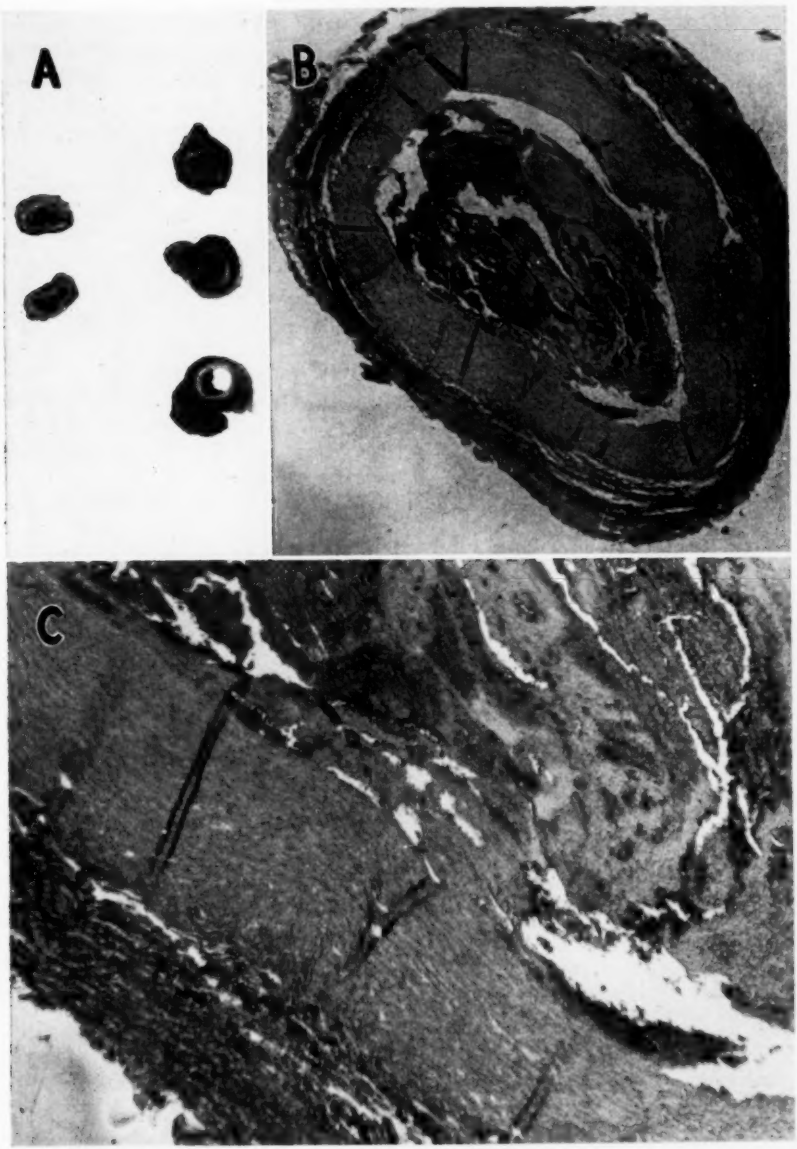

Fig. 5.—*A*, photographs showing thrombus in left common carotid artery; *B* (× 6.6) and *C* (× 30), photomicrographs of thrombus of the artery shown in *A*. The point of attachment of the thrombus to the vessel is clearly shown. Hematoxylin-eosin stains.

originators hoped to convert the vein into an arterial channel and thereby produce an accessory cerebral blood supply.[16]

In our patient the right common carotid artery was anastomosed with the right internal jugular vein, using the technique of Beck, McKhann, and Belnap. Immediately beforehand an angiogram had been made. The patient died 12 hours after operation. Autopsy revealed massive right intracerebral hemorrhage. The point of special interest in this case in connection with the present study is that a portion of the intimal and muscular wall of the artery had been sheared upward and projected into the lumen of the vessel (Fig. 4*B*). This injury was caused by the needle used for the angiography. A large thrombus was adherent to the free edge of the tissue. Had this man not died of intracerebral hemorrhage, he might have had complications as a result of the thrombosis of the carotid artery.

We have recently observed blindness due to occlusion of the central artery of the retina (Fig. 6) immediately after carotid angiography (left side) done by the open method, with 30 cc. of 40% iodopyracet solution introduced at operation through a polyethylene tube. This complication may have been due to the fact that the injection of isotonic sodium chloride solution through the tube and into the carotid artery was not begun immediately after insertion of the tube into the vessel and that the injection was not maintained continuously between the iodopyracet injections. A blood clot may have formed on the end of the tube while the flow was interrupted. The dislodgment of such a clot may have accounted for occlusion of the retinal artery. It is imperative to maintain complete continuity of flow of saline or Ringer's solution into the artery in order to avoid such complications.

As far as we know, the only recorded case of occlusion of the central retinal artery after cerebral angiography is one mentioned in a brief communication from the Association for Neurosurgical Studies to *The Journal of the American Medical Association*.[17]

> Christophe stressed the embolic origin of most complications (of cerebral arteriography). He discussed two cases; in one, a fragment of the embolus could be seen and followed with the ophthalmoscope in a branch of the central artery of the retina; in the other, an intracarotid injection reactivated an hemorrhagic focus in the basilar artery.

In this connection, it is interesting that Uihlein [12] described a case in which the patient "experienced an immediate ischemia of the superior half of each retina which cleared up in twenty-four hours, when blood was again seen in the arterioles

16. We have stopped using this operation after performing it upon nine mentally and physically retarded children (Tarlov, I. M.; Shuer, B.; Epstein, B.; Hirsch, E., and Nissen, R.: Brain Revascularization After Carotid-Jugular Anastomosis: Further Assessment by Angiography, S. Forum [1950], pp. 351-367, 1951), in whom no clinical improvement occurred. The chief effect of the operation was to divert the stream of arterial blood from the carotid artery to the internal jugular vein and thence to the transverse sinuses and the opposite internal jugular vein. The normal cerebral arterial channels were, for the most part, by-passed by this circuit.

Moreover, we have encountered severe progressive proptosis, subarachnoid hemorrhage, and fatal subarachnoid hemorrhage (Tarlov, I. M., and Grayzel, D.: Brain Hemorrhage After Carotid-Jugular Anastomosis: Implications of Changes in Walls of Blood Vessels, to be published) as complications of this operation. These sequelae result from dilatation and rupture of the veins subjected to unaccustomed arterial pressures.

17. Association for Neurosurgical Studies, Foreign Letters (Belgium), J. A. M. A. **145**:840 (March 17) 1951.

of the retina." He stated that he had "seen one other patient with a similar complication following angiography, prior to his coming to the Clinic, which had not cleared up and which had left a defect in the peripheral visual field." Torkildsen [18] also mentioned a case in which vision in the right eye was disturbed a

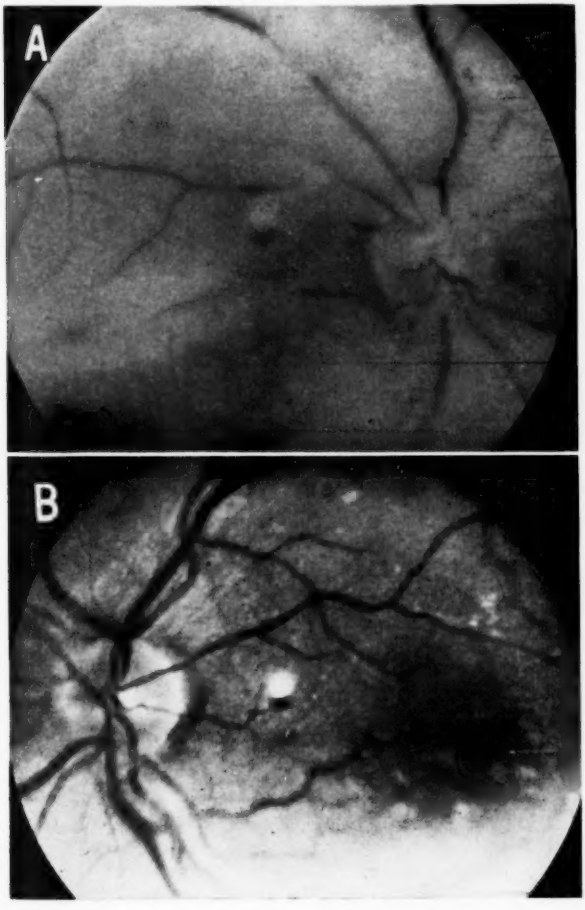

Fig. 6.—Retinal photographs showing evidence of occluded central retinal artery (*A*), with the control fundus in *B*.

18. Torkildsen, A.: Carotid Angiography, Acta psychiat. et neurol. (Supp.) **55**:32-33, 1949. Recently, Falls, Bassett, and Lamberts (Falls, H. F.; Bassett, R. C., and Lamberts, H. E.: Ocular Complications Encountered in Intracranial Arteriography, A. M. A. Arch. Ophth. **45**:623-626 [June] 1951) have recorded many ocular complications in a series of 80 patients subjected to intracranial arteriography. Ophthalmologic examinations were made both before

(Footnote continued on next page)

short time after the injection of iodopyracet ("perabrodil"). The visual disorder appeared as a monocular quadrantic defect (which had remained since) of the visual field. Ophthalmoscopic examination revealed vascular alteration, which possibly was due to embolism in the retinal artery.

In view of our demonstration of thrombosis of the carotid artery in three patients, it is possible that the cerebral infarcts that occurred in two of the fatal cases of Dunsmore, Scoville, and Whitcomb [11] were caused by thrombosis of the carotid artery, which had been damaged by the needle used in angiography. In both cases the authors made percutaneous injections. In another case, in which they also carried out percutaneous angiography, operation disclosed thrombosis of the internal carotid artery. These authors attributed these complications to vasospasm produced by iodopyracet. Our experience, however, indicates that thrombosis resulting from trauma to the vessel, as well as the injurious effect of iodopyracet on the vascular endothelium, is an important cause of serious seqnelae from iodopyracet angiography.[19]

We have performed 47 angiographic studies on 10 children, varying in age from 8 months to 13 years. On each occasion we injected 8 to 15 cc. of a 35% solution of iodopyracet. Total quantities of as much as 45 cc. were used for each angiography study. These patients were not hydrocephalic and suffered no ill effects from the iodopyracet injections. On the other hand, the three children who died after cerebral angiography were hydrocephalic. It is likely that hydrocephalus renders young children more susceptible to the toxic effect of the injections.

Broman, Forssman, and Olsson [20] have found that if the blood circulation to a part of the brain is retarded the necessarily prolonged application of the contrast medium is likely to injure the cerebral vascular endothelium. Possibly such a mechanism explains why iodopyracet is more injurious to the brain of the hydrocephalic than of the normal child.

Use of smaller quantities of iodopyracet in such patients might afford safe, yet satisfactory, vascular visualization. Moreover, it seems likely that the risks involved in cerebral angiography may be lessened by bearing in mind the investi-

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and after the procedure. Twenty patients showed retinal petechial hemorrhages. Pupillary dilatation, angiospasm of retinal vessels, and blindness due to optic neuritis in one patient were also observed. The complications were thought to result from vascular changes caused by allergic or toxic reactions. In their series there was one death, due to thrombosis of the internal carotid artery. These authors also cited a case of occlusion of the right temporal retinal artery following cerebral arteriography with iodopyracet, reported by Weekers (Weekers, R.: Accident vasculaire rétinien après artériographie cérébrale, Ann. ocul. **182**:926, 1949).

19. Dr. B. B. Shuer, working in this clinic, attempts to avoid the risk of trauma to the vessel wall during arteriography by substituting a polyethylene tube (2-mm. bore) for the rigid needle ordinarily employed. He exposes the internal carotid artery at operation and introduces an 18-gauge needle through the wall of the vessel, the lumen of which is partially occluded with a tape. He next runs the polyethylene tube a short way up into the vessel. The tube may be gently threaded farther upward into the vessel to avoid the possibility of its dislodgment if the patient is to be transported for the roentgenographic study. An added advantage of this technique is that, by using a long segment of polyethylene tube, the operator may stand at a considerable distance from the field of x-radiation.

20. Broman, T.; Forssman, B., and Olsson, O.: Further Experimental Investigations of Injuries from Contrast Media in Cerebral Angiography, Acta radiol. **34**:135-143, 1950.

gations of Broman, Forssman, and Olsson, who found that repeated injections of a contrast medium into the carotid artery tended to produce a summation effect if the intervals between the individual injections were short. They advised intervals of at least 15 minutes between injections.

Ziperman and associates [21] recently reported the effect of various anesthetic agents upon iodopyracet toxicity in the mouse. They found that the preliminary use of barbital and pentobarbital reduced the mortality from 70 to 19.1%. Before cerebral angiography with iodopyracet, therefore, premedication with these barbiturates seems indicated.

SUMMARY AND CONCLUSIONS

The use of total quantities of 20 to 32 cc. of a 35% solution of iodopyracet (diodrast®) for cerebral angiography in hydrocephalic children is hazardous.

The toxicity of iodopyracet in two of our fatal cases was manifested pathologically by swelling and hyperplasia of the vascular endothelium, with resultant narrowing of the lumina, and by perivascular hemorrhages. Regional damage of nerve tissue resulted.

Pronounced endothelial damage and thrombus formation in the carotid artery were observed at autopsy in three patients (one an adult) on whom angiography had been performed. In another patient homolateral blindness developed as a result of occlusion of the central artery of the retina, probably due to an embolus. The visual loss appeared immediately after the angiographic procedure. It seems likely that the risk of complications from cerebral angiography may be lessened by introducing a polyethylene tube or some other flexible catheter into the artery after puncturing it by the percutaneous or the open surgical technique. In a further attempt to prevent clotting within the vessel, a continuous slow injection of isotonic sodium chloride solution or Ringer's solution should be used. Certainly, in cerebral angiography the greatest care should be used to avoid unnecessary trauma to the wall of the blood vessel.

21. Ziperman, H. H.; Hughes, R. R., and Shumaker, H. B.: The Effect of Barbiturates and Other Drugs on Mortality from Diodrast in the Mouse, Angiology **1**:427-431, 1950.

EFFECTS OF FRONTAL LOBOTOMY ON THE MORPHINE-ABSTINENCE SYNDROME IN MAN

An Experimental Study

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ABSENCE of withdrawal signs in narcotic addicts following frontal lobotomy and abstention from drugs has been reported by several observers,[1] although a few have presented evidence to the contrary.[2] Published data are difficult to evaluate because in no instance were control observations made on the character and intensity of the physical dependence on narcotic drugs which was present prior to lobotomy, and because withdrawal of drugs was not abrupt in some cases, while in others observations were delayed beyond the time corresponding to the peak intensity of the opiate-abstinence syndrome.

The present study was designed to investigate this problem experimentally. Four subjects were selected, one of whom was a habitual narcotic addict with intractable pain in a phantom limb, while the other three were patients with schizophrenia of long standing who had not responded to treatment. For all four patients frontal lobotomy had been recommended for therapeutic reasons by a "lobotomy board," which included psychiatrists, a neurologist, and a neurosurgeon.

These experiments also provided an opportunity to investigate other problems, such as (*a*) the range and variation in the character and intensity of the morphine-abstinence syndrome; (*b*) the reproducibility of the morphine-abstinence syndrome

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1. Koskoff, Y. D.; Dennis, W.; Lazovik, D., and Wheeler, E. T.: The Psychological Effects of Frontal Lobotomy Performed for the Alleviation of Pain, A. Res. Nerv. & Ment. Dis., Proc. (1947) **27**:723, 1948. Mason, T. H., and Hamby, W. B.: Relief of Morphine Addiction by Prefrontal Lobotomy, J. A. M. A. **136**:1039 (April 17) 1948.

2. Dynes, J. B., and Poppen, J. L.: Lobotomy for Intractable Pain, J. A. M. A. **140**:15 (May 7) 1949. Hamilton, F. E., and Hayes, G. J.: Prefrontal Lobotomy in the Management of Intractable Pain, Arch. Surg. **58**:731 (June) 1949. Watts, J. W., and Freeman, W.: Frontal Lobotomy in the Treatment of Unbearable Pain, A. Res. Nerv. & Ment. Dis., Proc. (1947) **27**:715, 1948.

in a given subject; (*c*) the reactivity of the autonomic nervous system in response to the stress of abrupt withdrawal of morphine in schizophrenic patients who had acquired physical dependence on the drug; (*d*) the effects of single and repeated doses of morphine, and of the physiologic stress associated with the morphine-abstinence syndrome, on the behavior of schizophrenic patients; (*e*) comparative rates of development of tolerance to the effects of regular, repeated injections of increasing doses of morphine in nonaddicts and in patients with previous histories of morphine addiction (former addicts); (*f*) the relation of physical dependence on morphine to motivated behavior directed toward obtaining the drug, and (*g*) the functional relation of the anterior portion of the frontal lobes to the physiologic aspects of the morphine-abstinence syndrome and to motivation.

REPORT OF CASES

CASE 1.—A white man aged 48 complained of severe pain in a phantom limb, which dated from traumatic amputation of the right upper extremity at the shoulder in a railroad accident in childhood. Repeated excisions of "neuromas" at the stump and thoracic sympathectomy on the right side had failed to relieve his symptoms. Except for temporary "cures," he had been addicted to morphine, dihydromorphinone hydrochloride U. S. P. (dilaudid®), diacetylmorphine (heroin), and other opiate-like drugs almost continuously during the past 20 years. On the present admission, he was addicted to morphine, and attempts to relieve his pain by substitution of other drugs and five electroshock treatments were unsuccessful. After continuous administration of morphine sulfate (stabilization dose, 30 mg. four times daily) for 97 days, right unilateral frontal lobotomy was performed, with the use of local anesthesia, by a modification of the Lyerly technique through a superior frontal burr hole (this technique was employed in all lobotomies which were performed in the present study). After operation, morphine injections were continued as before. The patient's pain and phantom limb disappeared immediately after operation, and during the first three or four postoperative days he was lethargic and apathetic and displayed little initiative. Subsequently, however, these changes subsided, and, although he was again aware of a phantom limb, pain did not recur. Eighteen days after operation, morphine injections were terminated abruptly and completely. Within 24 hours he exhibited yawning, rhinorrhea, lacrimation, mydriasis, perspiration, restlessness, insomnia, fatigability, anorexia, vomiting, and a rise in rectal temperature, (1 degree [C.]), systolic blood pressure (22 mm. Hg), and cardiac rate (20 beats per minute). He was extremely anxious, demanded drugs, and threatened to commit suicide. The abstinence changes were relieved for about six hours by a single injection of 30 mg. of morphine sulfate, but they reappeared in only slightly diminished intensity later and another injection of morphine sulfate (20 mg.) was required. Complete withdrawal was subsequently accomplished in nine days by administration of morphine and of methadone derivatives in rapidly diminishing doses. He remained free from pain (but was still aware of the phantom limb) for five weeks, but thereafter morphine was again required. After 57 days of continuous, regular administration of morphine (stabilization dose, 30 mg. four times daily), left frontal lobotomy was performed, with local anesthesia, while morphine injections were continued on the same schedule as before. During the first five postoperative days, the patient was extremely lethargic and apathetic, and he wet his bed on two occasions. However, appetite remained unimpaired, and no gross memory defect could be demonstrated. Ten days after the second lobotomy morphine injections were discontinued abruptly and completely. During the next 36 hours he exhibited all the withdrawal signs noted previously but made no complaints. A single injection of 30 mg. of morphine sulfate was then administered because the patient vomited repeatedly and had lost 3.8 kg. in body weight since morphine had been withdrawn. The subsequent course was uneventful, and he was discharged from the hospital three weeks later, to resume his work as a railroad payroll clerk. According to the patient, he performed his duties well for five months, when the pain returned and he resumed the use of dihydromorphinone hydrochloride, in doses which finally reached a level of 4 mg. given 12 times daily (equivalent to 360 mg. of morphine a day). After self-readdiction for five weeks, he returned voluntarily to

the hospital, where narcotics were withdrawn rapidly, but not abruptly, by the methadone substitution method. No difficulties were encountered during the withdrawal period, and the patient expressed surprise at the minimum degree of discomfort which he experienced during this time. At the time of this report, nine months after the second lobotomy, he states that he still has pain in the phantom limb, and he also complains of headaches. However, he does not ask for narcotics and shows little concern over his condition. Otherwise, repeated physical and neurological examinations have revealed no significant changes from his preoperative status.

Case 2.—A white man aged 29 with schizophrenia (paranoid type) of at least eight years' duration was suspicious, combative, and assaultive; he had delusions and auditory hallucinations, used neologisms and "word salads," and displayed bizarre thinking, affectivity, and mannerisms. Insulin coma and electroshock therapies had failed to alter his condition. Single subcutaneous injections of morphine sulfate, in doses of 10 to 20 mg., produced little change in the patient's behavior. If undisturbed, he exhibited some drowsiness, but was instantly aroused by questioning, and displayed essentially the same incoherence of speech and lability of affect and psychomotor activity that were present before medication. Lowering of the body temperature (0.2 to 0.5 degree [C.]) and pulse rate (6 to 40 beats per minute) occurred consistently after such single doses of morphine, while effects on the respiratory rate, systolic blood pressure, and size of pupils were irregular. Vomiting was not observed. After these preliminary observations, morphine sulfate was administered continuously and regularly for 100 days (stabilization dose, 60 mg. four times daily). The patient tolerated this dose schedule without difficulty, except that during this period he lost about 10 kg. in body weight. Occasionally, routine observations revealed pronounced hypotension (80 to 90 mm. Hg systolic), bradycardia (30 to 40 beats per minute), and decrease in respiratory rate (8 to 10 per minute), but the patient was always responsive and exhibited no signs of distress. During this period the patient became somewhat less combative, but his psychiatric status remained otherwise essentially unchanged. A "test withdrawal" was then made by discontinuing injections of morphine abruptly and completely for 40 hours. During this time the patient exhibited yawning, lacrimation, rhinorrhea, mydriasis, fatigability, insomnia, anorexia, vomiting, rise in body temperature (1 degree [C.]), and loss of 3 kg. in body weight. Concomitantly with the development of the morphine-abstinence syndrome, the patient became more tractable and ceased to display his usual menacing, combative attitude. He complied with instructions, but replies to questions remained unintelligible. After the "test withdrawal," morphine injections were resumed as before, and the patient's behavior returned to the pre-withdrawal pattern. Two weeks later bilateral frontal lobotomy was performed, with the patient under intravenous thiopental sodium (4 gm.) anesthesia, supplemented with nitrous oxide-oxygen inhalations. Morphine was withheld for 40 hours after operation; after recovery from the anesthetics, the patient exhibited yawning, lacrimation, rhinorrhea, perspiration, and a moderate degree of restlessness, but other withdrawal signs were absent. Morphine injections were then resumed (60 mg. four times daily) for one week, when they were discontinued abruptly and completely. A very severe morphine-abstinence syndrome then ensued, the intensity of which reached a peak 72 to 96 hours after the abrupt withdrawal of the drug. During this period the patient exhibited all the signs noted in the "test withdrawal"; in addition, he vomited repeatedly and lost 9.5 kg. in weight in four days, after which a dramatic alleviation of the abstinence changes was effected by a single injection of 30 mg. of morphine sulfate. The patient's subsequent course was uneventful. During the first four days after bilateral frontal lobotomy the patient exhibited little spontaneity and wet his bed on several occasions. Speech remained incoherent, but he displayed none of his former combative attitudes. He ate well and began to display initiative and interest in his surroundings about the fifth postoperative day. After recovery from the final withdrawal period he continued to show steady improvement in speech, affect, ideation, and behavior. Six months after operation he was neat and tidy, worked several hours a day in the hospital laundry, greeted nurses and physicians in a friendly way, and asked when he would be discharged. In contrast to his behavior prior to lobotomy, he was able to engage in sustained activity in the occupational therapy department and showed particular interest in leather-tooling projects. However, there still appeared to be some poverty of ideas, and the patient's affect was flattened. At no time during the study did the patient ever display any interest in, or craving for, drugs of any sort, even when he exhibited severe abstinence changes.

CASE 3.—A white man aged 62 with schizophrenia (hebephrenic type, with deterioration) of at least 30 years' duration, was disheveled, untidy and incoherent and displayed incessant hyperactivity. He opened and closed his jaw continuously, shuffled about constantly, swallowed cigaret butts and other trash, smeared food, and destroyed furniture. He frequently appeared to be hallucinating and often "barked" or "bellowed" for no apparent reason. Standard therapy, including a course of electroshock treatments, had failed to alter his condition. Single subcutaneous injections of 10 to 20 mg. of morphine sulfate produced only slight and irregular changes in physiologic variables and no discernible changes in behavior. After these preliminary observations, morphine sulfate was administered regularly and continuously for 105 days (stabilization dose, 60 mg. four times daily). During this time he lost only about 2 kg. in body weight, and there was no significant change in his physiologic or psychiatric status, except that for a few days after each successive increase in dose he spent more time in bed. A 40-hour "test withdrawal" was then made by terminating injections abruptly and completely. During this period the patient exhibited yawning, lacrimation, goose flesh, mydriasis, occasional vomiting, and loss of 1.5 kg. in weight. Concomitantly with this rather mild morphine-abstinence syndrome, he became more tractable, and there was a notable reduction in such stereotyped behavior patterns as "barking" and "bellowing," opening and closing of the jaws, and devouring of trash. He also responded to questions, but these responses were bizarre. Morphine injections were then resumed as before, and his behavior pattern returned to the prewithdrawal status. Bilateral frontal lobotomy was performed 24 days later, under intravenous thiopental (1.5 gm.) anesthesia, supplemented with nitrous oxide-oxygen inhalations. During a 40-hour withdrawal period immediately after operation, and again after resumption of the previous morphine schedule for two weeks, the patient exhibited only lacrimation, mydriasis, and goose flesh. However, when morphine injections were again terminated abruptly after an additional 32 days of continuous, regular injections (stabilization dose, 80 mg. four times daily) yawning, goose flesh, mydriasis, muscle twitches, occasional vomiting, and loss of 2.5 kg. in body weight developed within 48 hours, after which the morphine-abstinence syndrome subsided rapidly. During the first two weeks after lobotomy the patient appeared to be easily fatigable and spent much time in bed. His appetite remained good, and, although noisy at times, other mannerisms, such as incessant opening and closing of the jaw and devouring of trash, were less prominent than before operation. Subsequently, his preoperative behavior pattern returned essentially unchanged, although a transient diminution in bizarre stereotyped activities was noted during the final withdrawal period. At no time during the study did the patient show any interest in, or desire for drugs.

CASE 4.—A white man aged 43 had schizophrenia (catatonic type) of about 15 years' duration. His behavior was extremely ritualized and negativistic, and he assumed bizarre "saluting" postures for hours, during which he mumbled incessantly. Standard treatments, including electroshock therapy, had failed to alter his condition. Single doses of 10 to 20 mg. of morphine sulfate produced no discernible effects on his behavior. Because of the patient's extreme negativism, reliable observations on physiologic variables could not be made. Continuous, regular subcutaneous injections of morphine sulfate were administered over a 30-day period (stabilization dose, 60 mg. four times daily), the rate of increase in dosage being the same as that used in experimental addiction studies on nonpsychotic former addicts. The patient tolerated these injections well, as far as could be judged by his behavior, and at no time was any evidence of overdosage of morphine observed. During the first two weeks of morphine administration he showed evidence of generalized itching of the skin, and a factitious dermatitis appeared on the chest and extremities. This responded to local symptomatic therapy and to antihistamine medication. A 40-hour "test withdrawal" was then made, during which the patient exhibited only mydriasis and goose flesh. His behavior was not changed. Continuous, regular injections of morphine were then resumed according to the previous schedule, and 27 days later bilateral frontal lobotomy was performed under intravenous thiopental-sodium (1.2 gm.) anesthesia, supplemented by nitrous oxide-oxygen inhalations. During a 40-hour period following abrupt withdrawal of morphine immediately after operation, and, again, after final, complete, and abrupt withdrawal of the drug following an additional 16-day period on the regular morphine schedule, the patient's abstinence changes consisted only of mydriasis and goose flesh. There were no significant changes in his behavior which could be attributed to the morphine-abstinence syndrome, but, presumably as a result of frontal lobotomy, he became increasingly tractable, less

agitated, and less manneristic and showed progressive improvement in contact during the subsequent eight months of observation. At no time did he show any interest in, or desire for, drugs.

COMMENT

Comparison of the morphine-abstinence syndromes which were observed in the four subjects studied in this investigation after abrupt withdrawal of the drug following periods of regular administration of morphine in comparable doses reveals the fact that the characteristics and intensities of this syndrome vary considerably from one subject to another, though they are fairly reproducible in any given person. In former addicts who volunteer for studies in drug addiction, a predictable relation can be established between the dose and duration of addiction, on the one hand, and the intensity of the morphine-abstinence syndrome, on the other.[3] In our experience, however, variations in the character and intensity of the morphine-abstinence syndrome, such as were observed in the present study, are also common in unselected former addicts. This may account in part for the conflicting reports in the literature regarding the effects of frontal lobotomy on the opiate-abstinence syndrome after withdrawal of drugs in narcotic addicts. The importance of control "test withdrawals" on the evaluation of the effects of any procedure on this syndrome is evident. It should be noted that the intensity of the morphine-abstinence syndrome reaches a peak between the 48th and the 96th hour after abrupt and complete withdrawal of the drug. Hence, observations which are made after this time, or after administration of even one or two doses of morphine or other narcotic, will impair the validity of such studies.

Experimental evidence indicates that the morphine-abstinence syndrome represents an "unmasking" of homeostatic mechanisms involving the autonomic [4] and somatic [5] portions of the central nervous system, as well as the pituitary-adrenal system,[6] which are developed in response to the depressant effects of repeated, regular injections of the drug. It is noteworthy that such homeostatic mechanisms may be unimpaired in schizophrenic patients. This is well exemplified by Case 2, in which the morphine-abstinence syndrome was as intense as any we have observed in nonpsychotic subjects.

Also, the rate at which tolerance to progressively increasing doses of morphine may be developed in schizophrenic patients who are not addicts appears not to be significantly different from that for former addicts, as illustrated by Case 4. It is, therefore, not necessary to invoke a hypothetical "residual" tolerance to explain the striking ability of nonpsychotic former addicts to increase their dose of morphine rapidly without serious effects. It should be borne in mind, however, that morphine may have a relatively slighter depressant effect on patients who are agitated and disturbed than on persons who are not.

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3. Andrews, H. L., and Himmelsbach, C. K.: Relation of the Intensity of the Morphine Abstinence Syndrome to Dosage, J. Pharmacol. & Exper. Therap. **81**:288, 1944.

4. Himmelsbach, C. K.: With Reference to Physical Dependence, in Symposium: Can the Euphoric, Analgetic and Physical Dependence Effects of Drugs Be Separated? Federation Proc. **2**:201, 1943.

5. Wikler, A.: Sites and Mechanisms of Action of Morphine and Related Drugs in the Central Nervous System, Pharmacol. Rev. **2**:435, 1950.

6. Fraser, H. F., and Isbell, H.: Relation of the Pituitary-Adrenal System to the Morphine Abstinence Syndrome, and the Effects Thereon of Cortisone and ACTH in Man, to be published.

Single doses of morphine had little effect on the behavior of schizophrenic patients, and regular, repeated doses of the drug in increasing quantities had equivocal effects in the direction of reducing their bizarre, stereotyped activities. However, the stress associated with the morphine-abstinence syndrome appeared to effect a temporary recession of bizarre mannerisms, stereotyped ritualistic behavior patterns, and assaultiveness in two of the three schizophrenic patients. The patients also appeared to be more responsive and tractable during the period

TABLE 1.—*Abstinence Changes After Abrupt Withdrawal of Morphine Following Right Frontal Lobotomy and After Left Frontal Lobotomy Three Months Later* *

	Day of Observation													
	After Right Frontal Lobotomy (Abrupt Withdrawal Delayed 18 Days After Operation)									After Left Frontal Lobotomy (Abrupt Withdrawal Delayed 10 Days After Operation)				
Abstinence Changes	1	2	3	4	5	6	7	8	9	1	2	3	4	5	6
Nonpurposive															
Yawning	xx	xx	..	..	..	..	..	..	..	xxx	xxx	..	..	..	..
Lacrimation	xx	xx	..	..	..	..	..	..	..	xxx	xxx	x	x	..	..
Rhinorrhea	xx	xx	..	..	..	..	..	..	..	xxx	xxx	x	..	..	..
Perspiration	xx	x	..	..	..	..	..	..	..	x	x	..	..	..	..
Goose flesh	..	x	..	..	..	..	..	..	..	..	..	..	..	..	..
Mydriasis	x	x	..	..	..	..	..	..	..	xx	xx	..	..	..	..
Tremors	..	x	..	..	..	..	..	..	..	..	x	..	..	..	..
Muscle twitches	..	..	..	..	..	..	..	..	..	x	xx	..	..	..	..
Excessive fatigability	xx	xx	x	x	.	..	..	..	..	?	?	..	..	..	..
Restlessness	xxx	xxx	..	..	..	.	..	..	..	x	xx	..	..	..	..
Insomnia	xx	xx	.	..	..	..	..	..	..	xx	xxx	..	..	..	..
"Yen sleep"	xx	xx	..	..	..	..	..	..	..	xx	xx	..	..	..	..
Anorexia	xxx	xx	x	..	.	..	..	..	..	xx	xx	..	..	..	..
Emesis	xx	xx	..	..	..	..	..	..	..	xx	xx	..	..	..	..
Weight loss	..	..	..	..	..	..	..	..	..	xx	xx	..	..	..	..
Rise in body temperature	x	..	..	..	..	..	..	..	..	x	x	..	..	..	..
Rise in blood pressure	xx	x	..	..	..	..	..	..	..	x	..	..	..	..	..
Rise in pulse rate	xx	xx	..	.	..	..	..	..	..	xx	..	..	..	..	..
Purposive															
Anxiety with craving	xxx	xxx	xx	x	..	..	..	..	x	..	?	..	..	..	..
for morphine; complaining; demand for drugs; threat of suicide	xxx	..	..	..	..	..	..	..	..	..	x	..	..	..	..
Narcotics administered	M. S. 30 mg.	M. S. 20 mg.	DAM 10 mg. M. S. 10 mg.	DAM 10 mg. METH 15 mg.	DAM 10 mg.	DAM 10 mg.	DAM 6 mg.	DAM 4 mg.	..	..	M. S. 30 mg.	..	..	..	..

* The patient (Case 1) was a man aged 48 with causalgia in a phantom limb and opiate addiction (recidivism). Prior to each withdrawal, the subject was stabilized on 30 mg. of morphine sulfate, administered subcutaneously five times daily. Morphine was administered continuously 97 days before the first, and 57 days before the second, withdrawal. M. S. indicates morphine sulfate; DAM, *d*-acetylmethadol (6-dimethylamino-4,4-diphenyl-3-acetoxyheptane); METH, methadone hydrochloride. Note the complete morphine-abstinence syndrome on abrupt withdrawal of the drug 18 days after right frontal lobotomy and the marked reduction in intensity of purposive, but not nonpurposive, abstinence changes on abrupt withdrawal of morphine 10 days after completion of lobotomy by an operation on the left side.

of abrupt withdrawal of morphine. Stress, of one sort or another, appears to be a factor common to many types of "organic" treatment in psychiatry, such as electroshock or chemical convulsant therapy, insulin coma, electronarcosis, and *Dauerschlaf*. The possibility that activation of physiologic homeostatic mechanisms may play a role in the therapeutic effects of such diverse treatments merits serious consideration.

The changes produced in schizophrenic patients by repeated injections of morphine and withdrawal of the drug illustrate well the fact that "physical dependence" is not synonymous with "addiction." In the psychiatric sense of

terms, none of the schizophrenic subjects could be classified as "addicts," since interest in the drug was not exhibited at any time, even by Patient 2, whose contact with reality was improved remarkably after frontal lobotomy. Evidently, "craving" for the drugs and "purposive" behavior designed to obtain it can be separated from the more "nonpurposive" changes which characterize the morphine-abstinence syndrome.

These observations furnish a basis for classifying the morphine-abstinence phenomena and evaluating the effects of frontal lobotomy thereon. In Table 1 are presented the changes which were observed after abrupt withdrawal of morphine

TABLE 2.—*Abstinence Changes Before, and on Two Occasions After, Bilateral Frontal Lobotomy* *

	Day of Observation									
	Prelobotomy		Postlobotomy							
	Test Withdrawal		Immediate Withdrawal		Withdrawal Delayed 1 Wk. After Lobotomy					
Abstinence Changes	1	2	1	2	1	2	3	4	5	6
Nonpurposive										
Yawning	xx	xxx	xx	xxx	xx	xxx	xxx	xx	x	..
Lacrimation	xx	xxx	xx	xxx	xx	xxx	xxx	x	x	..
Rhinorrhea	xx	xxx	xx	xxx	xx	xxx	xxx	xx	..	..
Perspiration	..	..	..	..	..	xx	xx	..	..	..
Goose flesh	..	x	x	..	..	x	x	..	..	..
Mydriasis	xxx	xxx	..	x	..	xxx	xxx	xxx	..	..
Tremors	..	..	..	..	..	xx	xx	..	..	..
Muscle twitches	..	..	x	x	..	xx	xx	..	..	..
Excessive fatigability	xx	xxx	..	x	x	xx	xxx	xxx	xxx	xx
Restlessness	..	..	xx	xx	..	xx	xx	xx	x	..
Insomnia	..	xx	..	..	..	xx	xxx	xx	..	..
"Yen sleep"	..	xx	..	..	..	xx	xxx	xx	..	..
Anorexia	x	xx	..	..	..	xx	xxx	xxx	..	..
Emesis	x	x	..	..	..	..	x	xxx	xx	..
Weight loss	..	xx	..	..	..	xxx	xx	x	..	..
Rise in body temperature	xx	x	..	..	..	x	x	xx	x	..
Rise in blood pressure	..	..	..	..	..	..	..	..	..	..
Rise in pulse rate	..	..	..	..	..	..	..	..	..	..
Lessening of psychotic stereotyped behavior	xx	xx	xxx	xxx	xx	xxx	xxx	xxx	xx	xx
Purposive										
Craving for and active seeking of morphine	..	..	..	..	..	..	..	..	..	..
Morphine administered	..	..	..	..	..	..	..	..	30 mg.	..

* The patient (Case 2) was a man aged 29 with schizophrenia, paranoid type. Before each withdrawal (abrupt), the subject was stabilized on 60 mg. of morphine sulfate given four times daily. Regular subcutaneous injections of morphine were begun 106 days prior to the "test withdrawal" and were continued until final withdrawal except for 40 hours immediately after lobotomy, when no drugs were administered aside from the operative anesthetics (thiopental sodium, given intravenously, and a nitrous-oxide-oxygen mixture by inhalation). Note the pronounced attenuation of abstinence changes when abrupt withdrawal was carried out immediately after lobotomy, and the reappearance of intense abstinence changes after resumption of regular morphine injections and abrupt withdrawal of the drug one week later.

after right, and subsequently left, frontal lobotomy in Case 1. It is evident that unilateral lobotomy had no significant effect on either the "purposive" or the "nonpurposive" abstinence changes. Completion of lobotomy by a subsequent operation on the left side practically abolished the "purposive" abstinence changes, while the "nonpurposive" changes were unaffected. The inefficacy of unilateral frontal lobotomy in abolishing the craving for morphine appears to be contrary to the observations of Scarff.[7] However, it should be noted that in our experi-

7. Scarff, J. E.: Unilateral Prefrontal Lobotomy for the Relief of Intractable Pain and Termination of Narcotic Addiction, Surg., Gynec. & Obst. **89**:385, 1949.

ments abrupt withdrawal of morphine was delayed until the patient recovered from the apathy and general unresponsiveness which were associated with the acute effects of the operation.

That such acute, transient effects of frontal lobotomy play an important role in the modification of the morphine-abstinence syndrome is illustrated in Table 2. In comparison with the effect in "test withdrawals," the nonpurposive features of the morphine-abstinence syndrome were markedly reduced in intensity when abrupt withdrawal was carried out simultaneously with frontal lobotomy, but they were unaltered, or perhaps intensified, when abrupt withdrawal of the drug was carried out one week later, after the initial lethargy and unresponsiveness of the patient had largely disappeared.

It appears, therefore, that effects of the operation other than the severance of frontothalamic radiations per se were responsible for the attenuation of the nonpurposive features of the morphine-abstinence syndrome when abrupt withdrawal was carried out simultaneously with lobotomy. While no conclusive data are available at present, it may reasonably be inferred that "cerebral shock" or "diaschisis"[8] may account for such effects, since early after the onset of hemiplegia due to vascular lesions,[9] or after ablation of the premotor cortex,[10] temporary autonomic reflex paralysis may supervene, even though there may be no impairment of vital autonomic functions, such as those which regulate respiratory rate and blood pressure levels. After recovery from such initial effects, autonomic reflex activity may be enhanced, as indicated by the observations of Rinkel and associates,[11] who reported that 4 to 120 days after frontal lobotomy vascular responses to epinephrine and to carotid-sinus stimulation were more marked than before operation. Similar studies on patients during the first few days after frontal lobotomy have not been reported, but it is well known that during this early period most lobotomized patients are apathetic and show few behavioral responses to stimuli. It seems reasonable to infer, therefore, that the absence of withdrawal signs in lobotomized narcotic addicts, which has been reported by some observers,[1] may be due in part to the common practice of withdrawing narcotics just prior to or immediately after operation. By the time the patient has recovered from "diaschisis" the peak intensity of the morphine-abstinence syndrome will have passed, and few changes may be discovered subsequently by casual observation.

The cortical areas which were undercut in the present studies could not be determined precisely. However, an approximate estimate was obtained by performing the operation on a cadaver and subsequently examining the brain (Figure). As determined by this method, the plane of lobotomy extended from a point on the middle frontal gyrus about 5 cm. posterior to the frontal pole, downward in an oblique direction to the orbital surface of the prefrontal region,

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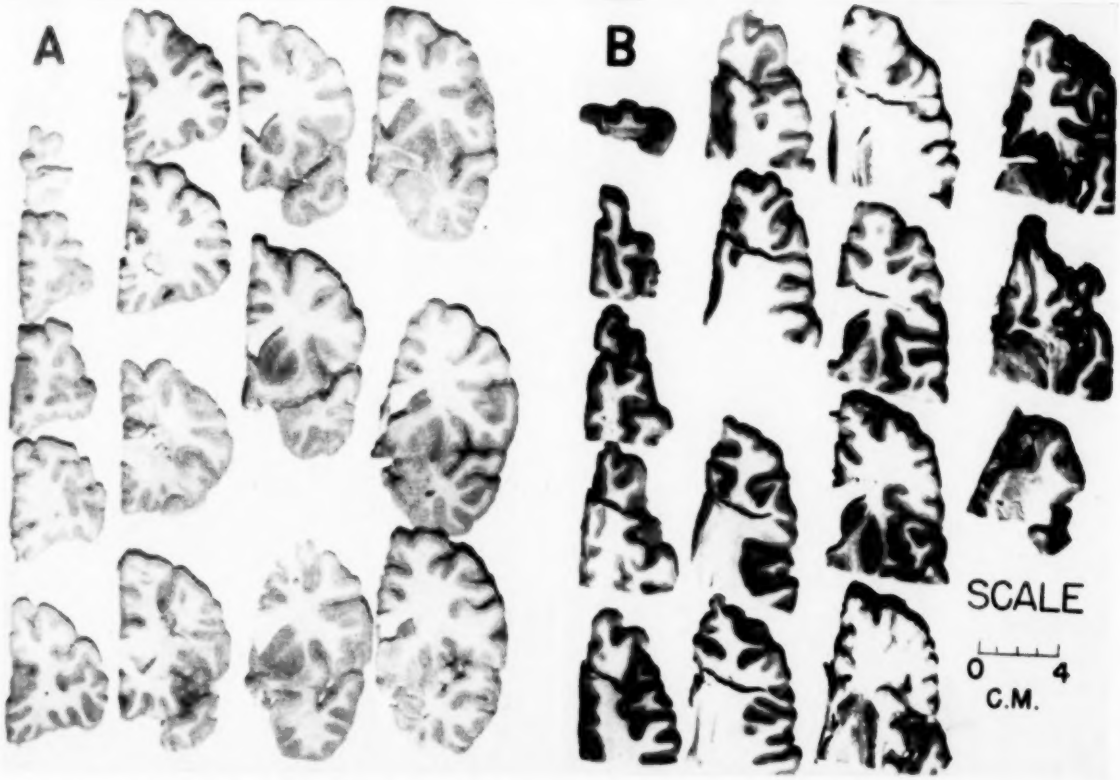
8. Grinker, R. R., and Bucy, P. C.: Neurology, Ed. 4, Springfield, Ill., Charles C Thomas, Publisher, 1949, p. 552.

9. Kennard, M. A.: Autonomic Function, in The Precentral Motor Cortex, Edited by P. C. Bucy, Illinois Monographs in the Medical Sciences, Vol. 1 to 4, University of Illinois Press, Urbana, Ill., 1944, p. 296.

10. Kennard, M. A.: Vasomotor Disturbances Resulting from Cortical Lesions, Arch. Neurol. & Psychiat. **33**:537 (March) 1935.

11. Rinkel, M.; Greenblatt, M.; Coon, G. P., and Solomon, H. C.: Relation of the Frontal Lobe to the Autonomic Nervous System in Man, Arch. Neurol. & Psychiat. **58**:570 (Nov.) 1947.



Sections of fixed brain after bilateral frontal lobotomy on a cadaver, through superior frontal burr holes in the skull. *A*, succesive coronal sections of the right frontal lobe at intervals of about 3 mm., beginning anteriorly with a section in the upper left-hand corner and reading down. Note the oblique plane of section, undercutting the superior and lateral portions of the anterior frontal cortex and the rostral orbital portion of the frontal lobes. *B*, successive horizontal sections of the left frontal lobe, with intervals as in *A*. Note that undercutting is complete medially to laterally. Thalamic radiations to and from the posterior orbital cortex may have been left intact.

and passed just anterior to the rostral end of the cingulate gyrus. The superior and lateral portions of the anterior frontal cortex were undercut completely, while most of the radiations from the posterior orbital cortex probably remained intact.

It may be concluded, therefore, that the integrity of the reciprocal pathways from the thalamus to the superior and lateral portions of the anterior frontal lobes and the rostral orbital cortex is not essential for the mechanisms which subserve the "nonpurposive" features of the morphine-abstinence syndrome. The "purposive" components of this syndrome are, however, dependent on the integrity of such pathways. These conclusions are in accord with the results of the studies in animals. Well-defined morphine-abstinence syndromes can be produced in a number of species, and these phenomena have been demonstrated in chronic decorticate and spinal dogs.[12] Such investigations have shown that the genesis of the morphine-abstinence syndrome is related, at least in part, to changes in the organism which are independent of symbolic significance. That the morphine-abstinence syndrome may be conditioned to meaningful stimuli has been suggested on theoretical grounds,[12] and a number of former addicts have reported that long after withdrawal of drugs they have observed in themselves subjective and objective changes which resemble those they experienced during the morphine-abstinence syndrome, when they found themselves in a situation which formerly would have been conducive to relapse. However, the results of the present investigation cannot contribute to a solution of this problem, since patients with frontal lobotomy are not "decorticated" and can respond to meaningful, as well as to nonmeaningful, stimuli. Nor can the "purposive" features of the morphine-abstinence syndrome be related to meaningful factors alone, even though they are markedly reduced by frontal lobotomy, for self-regulatory, goal-directed behavior may be related to such "organic" needs as hypothyroidism, hypocalcemia, and hypoadrenalism.[13]

However, the present studies do suggest that functions which are integrated in the frontal lobes are related to those which subserve "motivated" behavior in man. Indeed, many of the deficits which follow frontal lobotomy may be ascribed to reduction of "motivation." This inference is supported, though not proved, by the work of Pribram,[14] who demonstrated that the hunger-motivated performance of lobotomized baboons in a delayed-response situation was improved by procedures which promoted food intake (administration of pentobarbital or insulin, or reduction of environmental temperature) and was impaired by procedures which reduced food intake (administration of amphetamine, elevation of environmental temperature, or prefeeding).

An alternative explanation of the reduction of the "purposive" features of the opiate-abstinence syndrome by frontal lobotomy in narcotic addicts may be based

12. Wikler, A.: Recent Progress in Research on Neurophysiologic Basis of Morphine Addiction, Am. J. Psychiat. **105**:329, 1948.

13. Richter, C. P.: Total Self-Regulatory Functions in Animals and Human Beings, in Harvey Lectures, 1942-1943, Lancaster, Pa., Science Press, 1943, p. 63.

14. Pribram, K. H.: Some Physical and Pharmacological Factors Affecting Delayed Response Performance of Baboons Following Frontal Lobotomy, J. Neurophysiol. **13**:373, 1950.

on the concept of "anosognosia." Weinstein and Kahn [15] suggested that the denial of obvious illness in patients with organic brain damage represents a crude defense mechanism which is not normally utilized when brain function is intact. However, to validate the hypothesis that "anosognosia" accounts for the indifference which is associated with the opiate-abstinence syndrome in narcotic addicts after frontal lobotomy, it would be necessary to demonstrate that the same changes occur in patients with comparable damage to parts of the brain other than the frontal lobes.

In the light of these observations, it is evident that the reduction by frontal lobotomy of craving for drugs and of purposive behavior designed to obtain them cannot be cited as evidence of the "organicity" or "psychogenicity" of these features of the opiate-abstinence syndrome. While consideration of the subjective and physiologic aspects of these phenomena may be useful in understanding and in treating addicted patients, inferences regarding etiology which are based on the reaction pattern alone are heuristically unwarranted.

SUMMARY AND CONCLUSIONS

Continuous, regular subcutaneous injections of morphine sulfate in increasing doses up to a stabilization level of 30 to 80 mg. four times a day were administered to one habitual narcotic addict with pain in a phantom limb and to three patients with schizophrenia of long standing, whose condition did not improve after standard therapies and for whom frontal lobotomy was indicated for therapeutic reasons. The morphine-abstinence syndromes which followed temporary or permanent abrupt and complete withdrawal of the drug were studied quantitatively immediately after frontal lobotomy and again 7 to 46 days after the operation. In the three schizophrenic patients, these morphine-abstinence syndromes were compared with the results of control "test withdrawals" which were made prior to frontal lobotomy in each case.

Individual factors appeared to modify considerably the qualitative and quantitative characteristics of the morphine-abstinence syndrome in different patients, but this syndrome was reproducible to a remarkable degree in any one subject. Variations in the rates of development of tolerance to the effects of increasing doses of morphine, and in the intensities of the morphine-abstinence syndrome did not differ significantly in the schizophrenic patients from those which have been observed in nonpsychotic former addicts.

"Physical dependence" is not synonymous with "addiction," since none of the schizophrenic patients exhibited interest in, or craving for, morphine at any time during the study.

Temporary recessions of bizarre mannerisms and stereotyped abnormal patterns of behavior were observed in two of the three schizophrenic patients concomitantly with the development of the morphine-abstinence syndrome. This is interpreted as a nonspecific response to "stress," which may also play a role in the therapeutic effects of "organic" treatments in psychiatry.

Bilateral frontal lobotomy reduced markedly the "purposive" features of the morphine-abstinence syndrome but did not affect the "nonpurposive" abstinence

15. Weinstein, E. A., and Kahn, R. L.: The Syndrome of Anosognosia, Arch. Neurol. & Psychiat. **64**:772 (Dec.) 1950.

changes if abrupt withdrawal of morphine was delayed as little as one week after operation. When withdrawal of morphine was carried out coincidentally with bilateral frontal lobotomy, the "nonpurposive" changes were definitely attenuated, possibly because of temporary reduction in reactivity of the autonomic nervous system, due to "diaschisis."

Integrity of reciprocal pathways from the thalamus to the superior and lateral areas of the anterior frontal cortex and to the rostral orbital cortex is essential for the mechanisms which subserve the "purposive" components of the morphine-abstinence syndrome, but not for those which subserve its "nonpurposive" components.

The functional relation of the anterior frontal lobe to "motivation" is discussed.

The reduction in the "purposive" features of the morphine-abstinence syndrome by bilateral frontal lobotomy furnishes no data on which to base inferences regarding the "organicity" or "psychogenicity" of this phenomenon. Other experimental data, however, indicate that the genesis of both the "purposive" and the "nonpurposive" components of this syndrome is related, at least in part, to changes in the organism which are independent of symbolic significance, although theoretically such changes may become "conditioned" to meaningful stimuli, and there is some clinical evidence that this does occur.

EFFECT OF EPINEPHRINE ON CORTICAL AND BASAL ELECTROENCEPHALOGRAMS AND THE EOSINOPHILE COUNT

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THE PURPOSE of this study was to examine the cortical and basal electroencephalograms of subjects without clinical epilepsy or pituitary-adrenocortical disease who receive injections of epinephrine ordinarily sufficient to stimulate the secretion of adrenocortical hormone, as judged from the change in the absolute eosinophile count. These observations should indicate whether or not there is any relevant electroencephalographic activity, cortical or diencephalic, concomitant with adrenergic stimulation of the pituitary-adrenocortical system. Such information, it was hoped, might be helpful in determining what, if any, modifying influences the cortex and diencephalon have upon adrenocorticotrophic activity.

A search of the literature to find what effects of epinephrine on cerebral electrical activity might be expected indicates lack of agreement and unformity on the subject. Some authors report no appreciable effects of epinephrine on the electrogram [1] or electroencephalogram.[2] Others report definite effects on the cortical and basal electroencephalograms.[3] Some of these variations may be due to the different types of experimental subjects used, the differences in the doses of epinephrine administered, or the differences in the site from which the electrical activity was recorded.

Evidence that epinephrine induces discharge of corticotropin (adrenocorticotropic hormone; ACTH) from the adenohypophysis, which, in turn, regulates the secretory activity of the adrenal cortex to produce eosinopenia, has been thoroughly

From the Institute for Psychosomatic and Psychiatric Research and Training, Michael Reese Hospital, Chicago, and the National Institute of Mental Health, United States Public Health Service, Bethesda, Md.

1. Jasper, H., and Erickson, T. C.: Cerebral Blood Flow and pH in Excessive Cortical Discharge Induced by Metrazol and Electrical Stimulation, J. Neurophysiol. **4**:333, 1941.

2. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Effect on the Electroencephalogram of Certain Drugs Which Influence Nervous Activity, Arch. Int. Med. **60**:154 (July) 1937.

3. (*a*) Faure, J.: De quelques actions pharmacodynamique sur les potentiels électriques de la base due cerveau chez l'homme, Compt. rend. Soc. biol. **143**:391, 1949. (*b*) Greenblatt, M.; Funkenstein, D.; Miller, D., and Rinkel, M.: Electroencephalographic Patterns from the Base of the Brain, Am. J. Psychiat. **103**:749, 1947. (*c*) Grinker, R. R., and Serota, H. M.: Electroencephalographic Studies on Corticohypothalamic Relations in Schizophrenia, ibid. **98**:385, 1941.

reviewed elsewhere.[4] Thorn and co-workers [5] have developed a four-hour epinephrine test of pituitary and adrenocortical reserves and have indicated its usefulness and limitations. A reduction in the count of circulating eosinophiles in the blood of 50% or more four hours after an intramuscular injection of 0.3 mg. of epinephrine in fasting subjects has been found to be a sensitive indication of "normal" pituitary-adrenocortical stimulation and function. A drop in eosinophiles of less than 50% four hours after such a dose of epinephrine has been established as good evidence of pituitary or adrenocortical insufficiency due to primary disease or damage, such as Addison's disease or certain pituitary neoplasms.

Various investigations [6] have indicated that in a varying percentage of subjects without clinical evidence of pituitary or adrenocortical disease the absolute decrease in eosinophiles in a four-hour period after injection of epinephrine is less than 50%. Also, doses of epinephrine lower than 0.3 mg. or very low or very high initial eosinophile counts may lead to a higher percentage of false results.[6]

It was not the purpose of this investigation to elaborate on the conditions under which the four-hour epinephrine test gives misleading results, or otherwise to investigate any shortcomings of such a test which, for whatever reasons, may exist. Nor was it part of the experimental design of this study to employ this test to establish the presence of pituitary or adrenocortical disease, atrophy, or damage. Rather, it was the plan to employ such a test, not necessarily following a prescribed epinephrine dosage, to indicate, if possible, degrees or thresholds of reactability of the pituitary-adrenocortical system in response to adrenergic stress and to determine whether there are any electroencephalographic changes concomitant with stimulation of the pituitary-adrenocortical system.

Whether electroencephalographic observations might be a profitable avenue of research in determining the extent of any modifying influences the hypothalamus and cortex might have upon adrenocorticotrophic activity was of interest in this study. One of the mechanisms which has been postulated to explain how epinephrine may act to induce discharge of corticotropin from the adenohypophysis is that epinephrine may act directly on effector cells in the pituitary or in the hypothalamus and that hypothalamic stimulation may, in turn, activate the pituitary.[4]

4. (*a*) Dalton, A. J., and Selye, H.: Blood Picture During the Alarm Reaction, Folia hæmat. **62**:397, 1939. (*b*) Sayers, G.: Regulation of the Secretory Activity of the Adrenal Cortex, Am. J. Med. **10**:539, 1951. (*c*) Selye, H.: Physiology and Pathology of Exposure to Stress: A Treatise Based on the Concepts of the General-Adaptation-Syndrome and the Diseases of Adaptation, Montreal, Acta, Inc., 1950; (*d*) General Adaptation Syndrome and the Diseases of Adaptation, Am. J. Med. **10**:549, 1951; (*e*) General Adaptation Syndrome and the Diseases of Adaptation, J. Clin. Endocrinol. **6**:117, 1946. (*f*) Thorn, G. W.: Advances in the Diagnosis and Treatment of Adrenal Insufficiency, Am. J. Med. **10**:595, 1951.

5. Recant, L.; Hume, D. M.; Forsham, P. H., and Thorn, G. W.: Studies on the Effect of Epinephrine on the Pituitary-Adrenocortical System, J. Clin. Endocrinol. **10**:187, 1950.

6. Madison, L.: Comparison of the Anterior Pituitary-Adrenal Cortical Stimulating Effect of U. S. P. Epinephrine, Synthetic L-Epinephrine and Nor-Epinephrine, J. Clin. Invest. **29**:789, 1950. Pellegrino, P. C.; Morris, G. M., and Trubowitz, S.: Eosinophile Response to Epinephrine and Nor-Epinephrine, Proc. Soc. Exper. Biol. & Med. **59**:67, 1945. Perlmutter, M., and Mufson, M.: Hypoglycemic and Eosinophilic Response to Insulin: A Test for Pituitary-Adrenal Insufficiency, J. Clin. Endocrinol. **2**:277, 1951.

Experiments have demonstrated that activation of the adenohypophysis is not dependent upon direct neural connections with the hypothalamus; section of the infundibulum does not interfere with the response of the pituitary gland to acute stress in the rat [7] or in the dog [5] or with the response to chronic exposure to cold in the rat.[8] These experiments do not rule out the possibility that a neurovascular connection, the "hypophyseal portal system," plays a part in the regulation of adrenocortical activity.[9] Furthermore, direct evidence that hypothalamic centers have a regulatory influence over pituitary-adrenocortical activity has been demonstrated in the dog,[10] rabbit,[11] and rat [12] by producing diencephalic lesions which abolish the usual eosinopenic or lymphocytopenic response to stressful stimuli. Barbiturate medication has been found to inhibit the response of the pituitary-adrenocortical system to a few specific types of stress, but not to all [13]; it will inhibit the response to cold, but not to epinephrine, histamine, hemorrhage, or heat. This effect of barbiturates has been thought to be due to a selective action of the drug on the hypothalamus. Although the hypothalamus appears to have modifying influences on pituitary-adrenocortical activity, the most persuasive evidence that neither direct neural nor neurovascular connections with the hypothalamus are essential for discharge of corticotropin from the adenohypophysis is the experiments which have shown that transplants of the adenohypophysis in the anterior chamber of the eye will discharge corticotropin in response to stress.[14] Electroencephalographic observations, particularly basal-lead recordings, have not been fully explored in investigations of influences of the central nervous system on pituitary-adrenocortical activity.

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7. Cheng, C. P.; Sayers, G.; Goodman, L. S., and Swinyard, C. A.: Discharge of Adrenocorticotrophic Hormone in the Absence of Neural Connections Between the Pituitary and Hypothalamus, Am. J. Physiol. **158**:45, 1949. Fortier, C., and Selye, H.: Adrenocorticotrophic Effect of Stress After Severance of the Hypothalamohypophyseal Pathways, ibid. **159**:433, 1949.

8. Uotila, U. U.: On the Role of the Pituitary Stalk in the Regulation of the Anterior Pituitary, with Special Reference to the Thyrotropic Hormone, Endocrinology **25**:605, 1939.

9. Harris, G. W.: Oestrous Rhythm: Pseudopregnancy and the Pituitary Stalk in the Rat, J. Physiol. **111**:347, 1950. Harris, G. W., and Johnson, R. T.: Regeneration of the Hypophysial Portal Vessels After Section of the Hypophysial Stalk in the Monkey, Nature, London **165**:819, 1950.

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14. (*a*) Cheng, C. P.; Sayers, G.; Goodman, L. S., and Swinyard, C. A.: Discharge of Adrenocorticotrophic Hormone from Transplanted Pituitary Tissue, Am. J. Physiol. **159**:426, 1949. (*b*) Fortier, C., and Selye, H.: Adrenocorticotrophic Effect of Stress After Severance of the Hypothalamohypophyseal Pathways, ibid. **159**:433, 1949. (*c*) McDermott, W. W.; Fry, E. G.; Brobeck, J. R., and Long, C. N. H.: Mechanism of Control of Adrenocorticotrophic Hormone, Yale J. Biol. & Med. **23**:52, 1950.

METHODS AND PROCEDURES

Several preliminary experiments were carried out to find a dosage and method of administration of epinephrine which would produce prominent, but not too severe, subjective reactions and signs of adrenergic stimulation and, at the same time, would not be likely to cause a pronounced fall in eosinophiles in every subject with clinically normal pituitary-adrenocortical reserves to be studied. A dose of 0.2 mg. of epinephrine injected intramuscularly, followed in 15 minutes by another injection of 0.2 mg. of the drug (total dose, 0.4 mg.), was found to be satisfactory, from the standpoint both of following any possible electroencephalographic changes with increasing adrenergic stimulation and of stimulating differentially the secretion of adrenocortical hormone in the types of subjects studied.

Subjects.—A rough selection of subjects was made. Subjects only in the middle-age range were used, their ages varying from 22 to 37 years, with an average of 28⅔ years. No subjects were studied with established or symptomatic pituitary or adrenocortical damage or insufficiency, with clinical epilepsy, or with acute symptomatic disease. Patients were acceptable who had some other chronic disease or who had recently recovered from an acute minor illness. All subjects were healthy enough, at the time of the testing, to be gainfully employed on a full-time basis—evidence that if symptomatic disease did exist, it was fairly well compensated for and was not disabling to the extent of interfering seriously with the performance of the usual occupational activities.

Actually, there was some uniformity in the source and occupation of the subjects; most of them were hospital employees, i. e., technicians, nurses, interns, residents, and research personnel.

Methods.—The electroencephalographic tracings were made with an eight-channel Offner electroencephalograph and ink-writing crystograph recorder. The gain was set at 8. No slow-frequency filter was used. Calibration signals at 30 and 100 μv. were routinely recorded.

Solder electrodes were applied with collodion in the usual manner to the frontal, parietal, and occipital regions and to both ear lobes. A special nasopharyngeal lead, described elsewhere,[15] was inserted through the nasal passage so that the electrode tip would impinge on the central apex of the nasopharyngeal vault, below the pituitary and diencephalic structures.

Eosinophile counts were made according to the method of Randolph.[16]

Routine Procedure.—A sample of venous blood was drawn just before the electroencephalographic recording was started. Then, with the subject lying supine, a recording of the electroencephalographic activity at rest was taken for 10 minutes. Then a "control" injection of sterile water was administered into the deltoid muscle, and another period of electroencephalographic recording was carried out for five minutes or more, if indicated. The second injection, 0.2 mg. of epinephrine intramuscularly, followed, and the electroencephalographic activity was observed and recorded for 15 minutes. The third injection, 0.2 mg. of epinephrine intramuscularly, was administered, and the electroencephalographic tracing was followed for another 15-minute period. Thus, the electroencephalogram was recorded for a total of 30 minutes after the first injection of 0.2 mg. of epinephrine, and the recording was done for a period of about 45 minutes from start to finish.

The objective and subjective reactions of the subjects were noted and tabulated.

Four hours after the first injection of epinephrine (3 hours 45 minutes after the second injection of epinephrine), a second sample of blood was drawn for the eosinophile count.

All tests were started in the morning at 9 or 10 a. m. and were terminated four hours later, with the drawing of the second sample of blood for the eosinophile count. None of the subjects was fasting, and all of them had lunch between the drawing of the first and the second sample

15. Gottschalk, L. A.: A Nasopharyngeal Lead of New Design, Electroencephalog. & Clin. Neurophysiol. **3**:511, 1951.

16. Randolph, T. G.: Differentiation and Enumeration of Eosinophils in the Counting Chamber with a Glycol Stain: A Valuable Technique in Appraising ACTH Dosage, J. Lab. & Clin. Med. **34**:1696, 1949

of blood for the eosinophile count. All the subjects carried on their usual routine of occupation during the interval between the termination of the electroencephalographic recording and the second drawing of blood.[17]

Three experiments in which the above procedure was followed, with only slight variations, were carried out.

EXPERIMENT 1.—Six subjects received synthetic *dl*-epinephrine hydrochloride.

EXPERIMENT 2.—Twelve other subjects received synthetic *l*-epinephrine (suprarenin bitartrate[®]).

EXPERIMENT 3.—Four subjects, all reacting with a decrease in eosinophiles greater than 40% in Experiment 2, had the same experimental routine repeated except that all three injections during the electroencephalographic recording were of sterile water; i. e., no epinephrine was administered.

RESULTS

EXPERIMENTS 1 and 2.—Since in our subjects no remarkable differences were noted in the ability of *dl*-epinephrine and *l*-epinephrine in the same doses to evoke the eosinopenic response, as can be seen by inspection of Table 2, the findings in the two groups of subjects (Experiments 1 and 2) are included together.

Effects of Epinephrine on Cortical and Basal Electroencephalograms.—1. Movement, muscle-tension, cardiovascular, and respiratory artifacts became more prominent in the electroencephalograms as the subjective and clinical signs of adrenergic stimulation progressed. These changes in electrical potential of noncerebral origin were more prominent from the basal electrode (Fig. 1).

2. In 7 of 18 subjects no notable changes of cerebral origin could be detected by inspection of either the cortical or the basal electroencephalogram. Four of these 7 subjects had resting (preinjection) electroencephalograms devoid of deviant slow or fast frequencies; three had rare to occasional runs of low-amplitude (30 μv. or less) slower frequencies (4 to 8 cps) before injection of epinephrine.

3. In 11 of 18 subjects, electroencephalographic changes were detected after injection of epinephrine, after artifacts of noncerebral origin were eliminated from consideration. Figure 2 illustrates some of these changes, most of them being of variable nature and of slight degree.

The observation data indicate that in the subjects in whom epinephrine-induced changes were noted the range in changes was as follows:

1. More prominent 8½-to-12-cps (alpha) activity, most notable in three subjects, in whom there was little or no activity within this frequency range in either the cortical or the basal electroencephalogram before epinephrine.

2. Mild increases in amplitude and occurrence of slower frequencies, generally of low amplitude (30 μv. or less). In five subjects whose resting electroencephalo-

17. It should be clear that the data obtained from the eosinophile counts cannot be compared strictly with the expected findings reported with the Thorn four-hour epinephrine test, for, instead of a single injection of 0.3 mg. of epinephrine, 0.2 mg. of the drug was injected initially, followed by another 0.2-mg. injection of epinephrine in 15 minutes. Also, before and during the test the subjects were not kept in a fasting state and were engaged part of the time in their usual routine of work. Nevertheless, those subjects who revealed a marked fall in their eosinophile count in the four-hour period, it is felt, can be considered to have had a definite stimulation of the pituitary adrenocortical system by the epinephrine, whereas in the other subjects, with little or no eosinopenia after epinephrine, there must have been a relative lack of activation of the pituitary-adrenocortical axis.

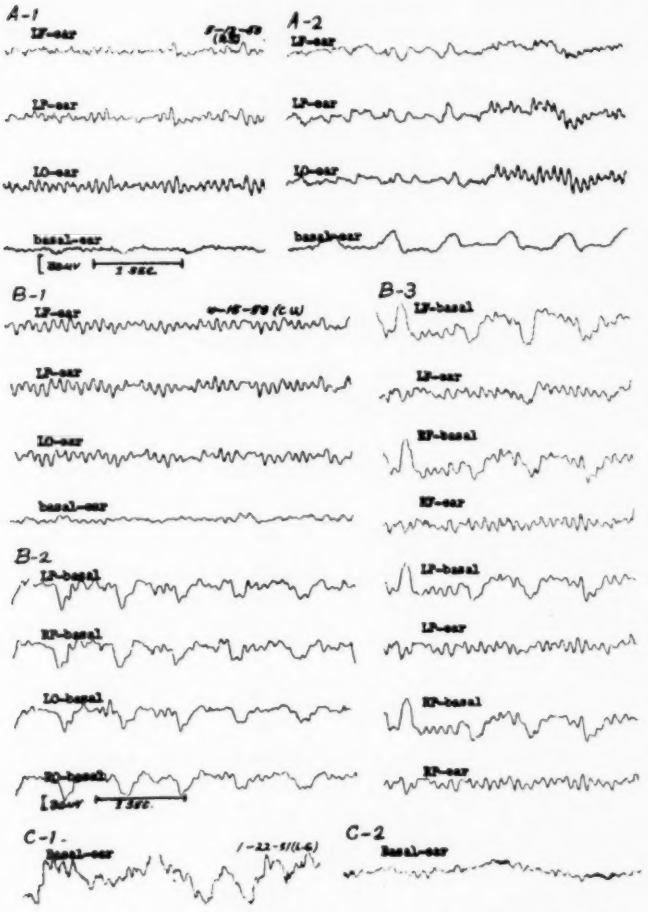

Fig. 1.—Representative records illustrating basal electroencephalographic artifacts: (*A-1*) Before injection of epinephrine. (*A-2*) Five minutes after second injection of epinephrine; the pulse wave shows prominently from basal-ear lead tracing.

(*B-1*) Before injection of epinephrine. (*B-2*) Five and one-half minutes after first injection of epinephrine; the pulse wave appears from all basal leads. (*B-3*) Seven and one-half minutes after first injection of epinephrine the pulse wave and movement artifacts arise from basal leads only.

(*C-1*) Resting basal record with subject breathing through nose. (*C-2*) Same basal electroencephalographic tracing a few minutes after subject was asked to breathe through mouth.

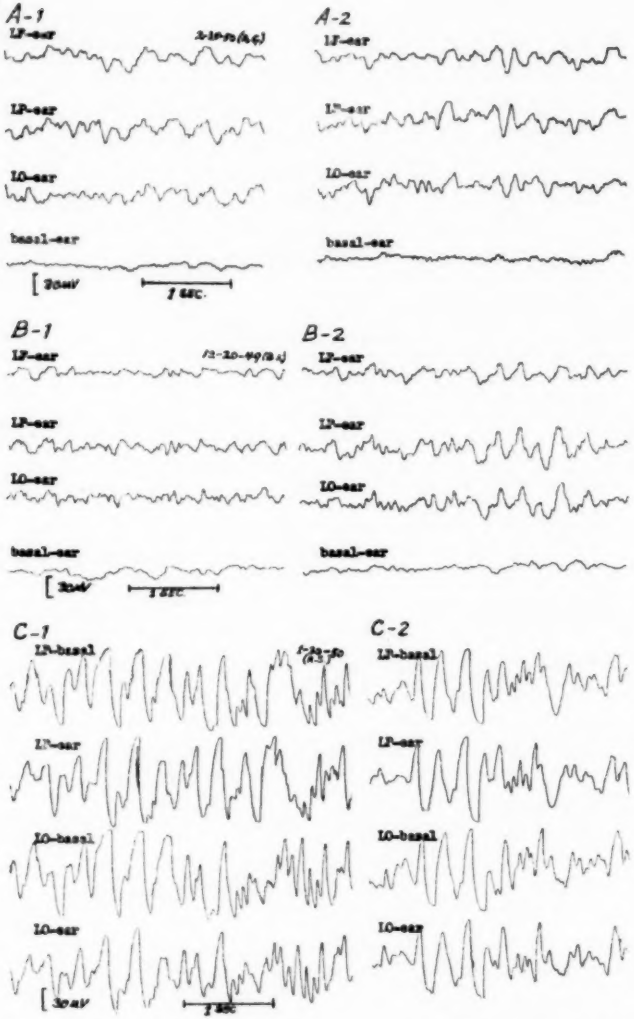

Fig. 2.—Negligible to discernible cortical electroencephalographic changes following injection of epinephrine.

(*A-1*) Before epinephrine; (*A-2*) six minutes after first injection of epinephrine.

(*B-1*) Before epinephrine; (*B-2*) ten minutes after second injection of epinephrine.

(*C-1*) Before epinephrine; note slow paroxysmal record of R. S., without history or symptoms of seizures. (*C-2*) Four and one-half minutes after second injection of epinephrine.

grams showed no low-amplitude (30 μv. or less), slower waves, low-amplitude frequencies of this sort (4 to 8 cps) developed after injection of epinephrine. In three subjects whose resting electroencephalograms revealed low-amplitude slower frequencies, slow frequencies of moderate amplitude appeared after administration of epinephrine. In one subject who showed slower frequencies of moderate amplitude before injection of epinephrine, waves of high amplitude (100 μv. or greater) developed after injection of epinephrine. However, one subject who had high-amplitude paroxysmal slow waves before injection of epinephrine showed a tendency toward a decrease in amplitude and occurrence of such paroxysms after injection of epinephrine.

3. Mild increase in amplitude and occurrence of faster frequencies. This occurred in one subject in whom the resting (preinjection) record showed low-amplitude, fast frequencies (18 to 24 cps).

The basal electroencephalographic changes tended to parallel the cortical electroencephalographic changes, but when waves of noncerebral origin were ruled out

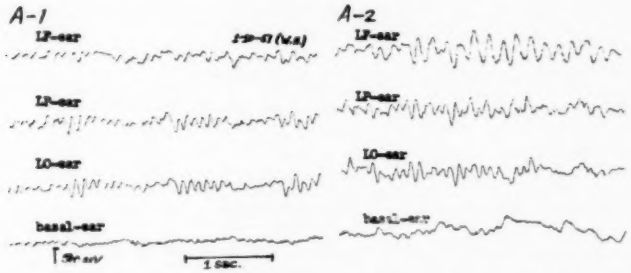

Fig. 3.—Representative samples of the electroencephalogram of subject W. H. during Experiment 3. (*A-1*) Resting record, before any injections. (*A-2*) One minute after first injection of sterile water; note 6-cps frequencies from frontal-ear leads.

the basal electroencephalographic changes were no more prominent than the cortical changes.

In 7 of these 11 subjects the electroencephalographic changes first appeared 5 to 10 minutes after the first injection of epinephrine; in the other four subjects, they appeared 5 to 10 minutes after the second injection of epinephrine.

EXPERIMENT 3.—The effect of the same routine as that in Experiments 1 and 2, with injections of sterile water substituted for the epinephrine injections, was investigated.

This control study indicated that there was a tendency in the electroencephalogram toward the development of more prominent 8½-to-12-cps (alpha) activity and more low-amplitude slower frequencies as the patient settled down and became more accustomed to the presence of the basal electrode and the experimental situation and became more relaxed. These changes during the control experiment in four subjects were generally not so pronounced as after injections of epinephrine and did not have any specific time relation to the injections. In one instance there were no detectable changes whatsoever. In another instance short runs of low-amplitude

slower waves appeared after the first injection of sterile water (Fig. 3). Changes in the basal electroencephalogram paralleled those in the cortical electroencephalogram (Table 1).

Subject W. H. (Table 1), not a member of the medical personnel, was unaccustomed to receiving injections but was not obviously tense or upset on such occasions. He did report mild subjective reactions during this control test, namely, slight shortness of breath. The considerable eosinopenia he had after receiving only sterile water suggests that for some subjects the experimental routine in itself constituted sufficient stress to evoke eosinopenia. It also suggests that electroencephalographic changes of the kinds observed in these experiments are not necessarily specific reactions to epinephrine.

However, in view of the limited aspects of this control experiment, the specificity of the changes in alpha frequency and amplitude and the prominence of slow waves in the electroencephalogram as reactions to the injection of epinephrine must be

TABLE 1.—*Effect of Experimental Routine with Injections of Sterile Water Substituted for Injections of Epinephrine* *

Subject	EEG Before Injections (Resting)	Electroencephalographic Changes After Injections	Eosinophile Drop (%)	
			With Epinephrine	With Sterile Water
O. L.	Regular, 10-cps waves	After third injection, occasional bursts of low-amplitude (30 μv.) 7-to-8-cps waves	−85	−29
W. H.	Regular, 11-cps waves	After second injection, more regular and frequent, 9 cps waves moderate amplitude, principally from frontoparietal leads	−65	+42
E. L.	9-cps waves and low-amplitude, faster frequencies (18-24 cps)	After second injection, more regular and frequent, 9 cps waves	−65	+42
R. S.	11-cps waves, and infrequent low-amplitude, 6-to-8-cps waves	No changes	−44	−8

* Basal electroencephalographic results are omitted because they paralleled cortical electroencephalographic changes.

considered questionable. It is believed that these experiments point up the importance of indirect, rather than of direct, effects as the basis for the present and previously reported electroencephalographic changes after epinephrine administration.

Effects of Epinephrine on the Eosinophile Count of 18 Subjects and Correlations with Electroencephalographic Patterns.—1. No definite changes or differences in the cortical or basal electroencephalograms occurred after the administration of epinephrine, either in subjects with a pronounced eosinophile fall or in subjects with none. No significant relation was found to exist between the occurrence or absence of electroencephalographic changes after epinephrine and the percentage drop in eosinophiles (chi-square value = 0.066).

2. A definite difference, however, was revealed between the resting (preinjection) cortical electroencephalograms of subjects who had a pronounced fall in eosinophiles and the electroencephalograms of subjects who did not. The more "normal" the preinjection cortical electroencephalogram, the greater the eosinopenia in response to a standard injection of epinephrine; the more deviant the electro-

encephalogram, even in minor particulars, such as low-amplitude (30 μv. or less) slower or faster frequencies, the slighter the eosinopenia in response to such a stressful stimulus.

TABLE 2.—*Percentage Change in Eosinophiles in Subjects Four Hours After Receiving 0.4 Mg. of Epinephrine Intramuscularly (0.2 Mg. in Two Doses 15 Minutes Apart)*

Subject	Age	Sex	Diagnosis	Resting Cortical EEG (Predominant and Characteristic Rhythm)	Eosinophile Count			Electroencephalographic Changes Detected After Epinephrine
					Hour		Percentage Change	
					0	4		
			dl-Epinephrine (6 Subjects)					
C. S.	26	F	No symptomatic disease	Regular, 10½ cps	110	22	−80	..
O. S.	37	M	Allergic rhinitis—asymptomatic	Low amplitude, 10 cps	128	60	−52	+
S. G.	25	F	No symptomatic disease	10 cps	213	125	−42	..
J. M.	27	M	Allergic rhinitis—asymptomatic	Fairly regular, low-amplitude 10 cps and occasional 5-6 cps	556	381	−31	..
M. K.	37	M	Gout	Irregular, 11 cps and low-amplitude 4-cps waves	103	94	−9	+
B. K.	24	M	No symptomatic disease	11½ cps and low-amplitude 3-4 cps	284	275	−3	..
			l-Epinephrine (12 Subjects)					
G. L.	33	M	No symptomatic disease	Regular 10 cps	110	16	−85	+
W. H.	27	M	No symptomatic disease	Regular 11 cps	194	63	−67	..
E. L.	22	F	Asymptomatic rheumatic heart disease	Fairly regular 9 cps and low-amplitude 18-24 cps	181	62	−65	+
C. U.	35	F	Anxiety neurosis	Fairly regular 11 cps	400	150	−63	..
L. G.	34	M	No symptomatic disease	Regular 10 cps	102	47	−54	+
R. G.	25	M	Recently recovered from infectious mononucleosis	Infrequent 8½ cps and low-amplitude 4 cps	169	97	−47	+
R. S.	23	M	No symptomatic disease	Regular 12 cps	791	440	−44	+
H. M.	35	M	Duodenal ulcer, generally asymptomatic	Infrequent 11 cps, low-amplitude 7 cps and LVS	150	90	−40	+
G. S.	25	M	? Mild hypothyroidism	Fairly regular 9 cps and low-amplitude 3-4 cps	94	78	−31	..
M. K.	28	M	Diabetes mellitus (labile)	Infrequent 10 cps and high-amplitude 2-6 cps	53	47	−11	+
W. W.	31	M	? Narcolepsy	Occasional 9½ cps and moderate amplitude 3-5 cps	86	91	+3	+
R. S.	22	M	No symptomatic disease	High amplitude, paroxysmal 3 cps and 6-12 cps	137	153	+11	+

In Table 2, the degrees of eosinopenia occurring in the subjects under conditions of Experiments 1 and 2 are tabulated, and the predominant and characteristic pattern of the cortical resting electroencephalogram of each subject is described. As examination of the table shows, there are occasional exceptions to the tendency of "normal" resting electroencephalograms to be associated with more pronounced eosinopenia after adrenergic stimulation.

For purposes of this study, "normal" or average electroencephalographic records were adjudged essentially on the basis of the classifications and findings of

Gibbs and Gibbs.[18] Frequencies ranging from 8 to ½ cps or from 12 to 36 cps or more were considered in the direction of deviance, as well as certain wave patterns, such as spiking, whereas the predominance of 8½-to-12-cps activity, low-voltage slow and low-voltage fast activity, absence of foci, absence of asymmetries, and absence of paroxysmal discharges were considered in the direction of average or "normal." When rhythms slower or faster than 8½ to 12 cps had an amplitude of 30 μv. or less, they were tabulated as "low-amplitude" frequencies and were considered to be an expression of slight deviance, although electroencephalographic records with such low energy output in these frequency ranges might ordinarily, for clinical purposes, be evaluated as without significant abnormalities. "Moderate amplitude" was used to designate potential variations roughly within the range of 40 to 90 μv.; "high amplitude" was used to designate voltages of activity of 100 μv. or greater.

COMMENT AND CONCLUSIONS

Effect of Epinephrine on the Cortical and Basal Electroencephalograms.—This study reveals that the kind and intensity of the adrenergic stimulation used under the conditions of these experiments had no discernible effects on the basal and cortical electroencephalograms of 7 of 18 subjects. Although 11 of the 18 subjects did have definite minor electroencephalographic changes, generally in the direction of more prominent 8½-to-12-cps activity or slight increases in the amount and amplitude of slower frequencies, these changes could not be attributed with any certainty to the direct or specific action of epinephrine on the central nervous system. In fact, in a control study in which the identical experimental routine was repeated with sterile water substituted for epinephrine in all injections, a tendency toward the increasing prominence of 8½-to-12-cps activity or slower frequencies was noted, although these were not generally of as great magnitude as with epinephrine.

In previous experimental studies reporting changes in cerebral electrical activity of an appreciable degree following stimulation with epinephrine, the direct effects of epinephrine on the central nervous system have not been clearly distinguishable from indirect effects. These indirect effects, as recorded on the electroencephalogram, may include cardiovascular, respiratory, neuromuscular, and other mechanical or electrical rhythms of noncerebral derivation appearing in the electroencephalogram. It is likely that most such artifacts recorded in the electroencephalogram as a result of the generalized systemic effects of epinephrine have been distinguished and separated by investigators in making a final evaluation of their electroencephalographic recordings. But other secondary, or indirect, effects of epinephrine on the central nervous system are extremely difficult to distinguish from primary, or direct, effects on the brain, namely, the hemodynamic and metabolic effects of the peripheral action of epinephrine, including increased pulse rate, increased stroke volume of the heart, increased blood flow, increased respiratory rate, and increased respiratory volume. The observations of Grinker and Serota [8c] and Greenblatt and

18. Gibbs, F. A.: Electroencephalography, Principal Patterns, Diagnostic Evaluation, Topic 49, in Solomon, H. C., and Yakovlev, P. I., Editors: Manual of Military Neuropsychiatry, Philadelphia, W. B. Saunders Company, 1944. Gibbs, F. A., and Gibbs, E. L.: Atlas of Electroencephalography, Cambridge, Mass., Addison-Wesley Press, Inc., 1950, Vol. 1, Methodology and Controls; Atlas of Electroencephalography, Cambridge, Mass., Lew A. Cummings Co., 1941.

his co-workers [3b] that electroencephalographic changes in the cortical and basal records were more prominent in subjects who had the more definite subjective and clinical signs of adrenergic overstimulation suggest that such peripheral side-effects may be significantly responsible for the electroencephalographic changes observed after stimulation with epinephrine. More evidence along this line is afforded by the experience of Jasper and Erickson,[1] who, in recording the electrogram of cats after intravenous injections of epinephrine, noted "no perceptible change or slight increase in electrical activity" from the posterior sigmoid gyrus, but shortly after the adrenergic stimulation they noted first an increase of blood pressure, and then an increase of cerebral blood flow, followed shortly by an increase of pH at the site of nerve tissue from which the electrogram was recorded. These observations, and our own findings, incline us to the view that the action of epinephrine on cerebral electrical activity may be largely indirect, through the widespread systemic reactions induced by the drug and the transient lag in restoring homeostatic equilibrium, rather than through a direct effect on the central nerve tissues.

Further studies will be necessary to evaluate the nature of the mechanism of action of epinephrine on the electroencephalogram and the degree to which direct and indirect factors are responsible for these changes. Certainly, when one is dealing with some of the minor electroencephalographic variations noted, a frequency-spectrum analyzer, as well as simultaneous measurements of other physiologic and biochemical responses to epinephrine, will be found useful in evaluating the electroencephalographic findings.

Electroencephalographic Patterns and Effects of Epinephrine on the Eosinophile Count.—The tendency toward greater eosinopenia after epinephrine injections of subjects with the more "normal" resting cortical electroencephalograms and the tendency of subjects with deviant electroencephalograms to have less eosinopenia after injection of epinephrine may be an expression of a functional integrative relation of two body systems—the central nervous system and the pituitary-adrenocortical system.

One cannot conclude from this finding, however, that the central nervous system has a modifying influence on adrenocorticotrophic activity, for the deviant electroencephalograms in some instances may equally well be a result of disturbance in adrenocortical regulation, or they may be entirely unrelated. Furthermore, the fact that no significant relation was found to exist between the occurrence or absence of electroencephalographic changes after epinephrine and the percentage decrease in eosinophiles is negative evidence for regulation of adrenocorticotrophic activity by the central nervous system.

Sayers [14a] has summed up the present status of our knowledge of the integrative functional relation between the central nervous system and the pituitary-adrenocortical system in the following statement:

> . . . It appears that neither direct neural nor neurovascular connections with the hypothalamus are essential for the discharge of ACTH from the adenohypophysis, although the possibility that the hypothalamus has a modifying influence upon pituitary adrenocorticotrophic activity has not been ruled out.

Though on the basis of our findings we cannot elaborate on this statement, our study offers a new, although obviously limited, avenue of investigation of the prob-

lem. Our findings do not indicate the primacy of one internal regulatory system over another in adaptation to stress. If anything, they suggest that regulation of the person's adaptive reactions to a stress is a complicated, and probably cooperative, mustering of multiple bodily resources unique to each individual.

Further exploration and verification of the effects of epinephrine on the cortical and basal electroencephalograms and the fluctuations in the eosinophile count are indicated.

SUMMARY

Two intramuscular injections of 0.2 mg. of epinephrine 15 minutes apart in 18 non-fasting subjects without clinical epilepsy or pituitary-adrenal disease failed to produce any notable or consistent changes in the basal and routine cortical electroencephalograms, either in subjects who had a pronounced decrease in eosinophiles four hours later or in those who had little or no decrease in eosinophiles.

No significant relation was found to exist between the occurrence or absence of electroencephalographic changes after administration of epinephrine and the percentage decrease in eosinophiles.

There was a trend toward resistance to eosinopenia in response to adrenergic stress in subjects with electrical activity other than alpha rhythm in the resting cortical electroencephalogram, and the subjects with more "normal" resting cortical electroencephalograms tended to have a greater eosinopenic response to the adrenergic stimulation.

The minor electroencephalographic changes that did appear in 11 of the 18 subjects after administration of epinephrine seem to be associated with indirect and nonspecific effects, rather than with direct effects, of epinephrine on tissues of the central nervous system.

Practical and theoretical considerations of the findings are discussed as they may be related to the problem of integrative functional relations between the central nervous system and the pituitary-adrenocortical system in health and in disease.

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PSYCHOSOMATIC ASPECTS OF MULTIPLE SCLEROSIS

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A CURRENT trend in medicine is toward a more integrated consideration of pathogenesis. This trend is based on a holistic concept of personality, which defines personality as an organism-environment system in which the total organism functions as a whole within its complex environment. The holistic concept of personality has been elaborated by Goldstein,[1] Angyal,[2] and Murphy.[3] Recently, Alexander and French,[4] in referring to the processes of adaptation, state:

> This adaption is the function of the central nervous system. In man we call this function "personality," which is but the sum of these integrated reactions of the total organism to its environment.

Angyal [2] defines the organism-environment system as follows:

> . . . It is, in principle, impossible to draw any line of separation in space between organism and environment. . . . There is no biological process which is determined entirely organismically or entirely environmentally; it is always a resultant of both factors.

Angyal [2] has considered in detail the various integrative processes which serve as the basis for the holistic concept of personality.

Until recently, psychosomatic studies of organic diseases of the nervous system have not been based on the holistic concept of personality. Psychic disturbances, including neurotic, psychotic, and intellectual personality changes, have long been observed in organic diseases of the nervous system but usually have been considered either as incidental associations with the somatic symptoms or as direct effects of damage to the brain. Although psychic disturbances can result from brain damage per se, they also may be manifestations of the tendency of a diseased organism to

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1. Goldstein, K.: The Organism, New York, American Book Company, 1939.
2. Angyal, A.: Foundations for a Science of Personality, New York, Commonwealth Fund, 1941.
3. Murphy, G.: Personality, New York, Harper & Brothers, 1947.
4. Alexander, F., and French, T. M.: Psychosomatic Medicine, New York, Ronald Press Co., 1948.

maintain some state of organism-environment integration. Goldstein [1] refers to this as a "tendency to ordered behavior." He describes the dynamics that "enable the organism to come to terms with environment at least in some way." Murphy [3] expresses the same mechanism, as follows: ". . . Even under gross impairment there is no deletion of parts but the reintegration of the individual at a new level."

In elaboration of the definition of personality as stated above, and on the basis of his studies of higher cortical functions,[5] Teitelbaum [6] has considered personality as an expression of integrative processes occurring in the cerebral cortex. In any traumatic situation, psychogenic or organic, disturbance of the normal cortical integrative processes occur, leading to their disintegration. Associated with the latter there occurs a reintegration of cortical processes on a lower level, involving a lower degree of integrative complexity than was possible originally. Such a reintegration results in a more limited range of adjustment of the organism within its environment. Goldstein [1] presents significant data pertaining to this more limited range of adjustment; Murphy [3] also discusses this phenomenon. Teitelbaum [6] has compared this disintegrative-reintegrative process to the concept of regression as used psychoanalytically. Hollos and Ferenczi [7] conclude, in a classic monograph, that the psychic disorders in dementia paralytica can be explained as "regressions to earlier levels of ego development." Regression refers to the purely psychological aspects of the mechanism under discussion; the process of disintegration-reintegration involves, in addition, the physiological aspects.

We shall use the broad principles of personality as a holistic organism-environment system for our consideration of four clinical case histories. Before these histories are presented, we shall review the pertinent literature in order to disclose how the problem of psychic disturbances in multiple sclerosis has been considered in the past.

The psychiatric manifestations of multiple sclerosis were recognized on a clinically descriptive basis by the turn of the century. The earlier publications of Seiffer,[8] Raecke,[9] and Ross [10] and the more recent report of Langworthy [11] indicate the extensive range of psychic symptoms in multiple sclerosis. Langworthy [11] found no characteristic psychiatric pattern in this disease. Wilson [12] comments further:

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7. Hollos, S., and Ferenczi, S.: Psychoanalysis and the Psychic Disorder of General Paresis, New York, Nervous & Mental Disease Publishing Company, 1925.

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9. Raecke, G.: Psychische Störungen bei der multipler Sklerose, Arch. Psychiat. **41**:482-518, 1906.

10. Ross, D.: Mental Symptoms in Disseminated Sclerosis, Rev. Neurol. & Psychiat. **13**:361-373, 1915.

11. Langworthy, O. R.: Relation of Personality Problems to Onset and Progress of Multiple Sclerosis, Arch. Neurol. & Psychiat. **59**:13-28 (Jan.) 1948.

12. Wilson, S. A.: Neurology, Baltimore, Williams & Wilkins Company, 1940, Vol. 1, pp. 166-168.

It is remarkable how diverse and even contradictory have been opinions relating to the mental symptoms of the disease, as regards their frequency and importance. No doubt its "mental symptomatology" does vary within the widest limits.

There have been attempts to establish a characteristic syndrome for the psychiatric manifestations of multiple sclerosis, despite the extreme variations noted clinically. Such classifications appear arbitrary and are of dubious value.

The publications of Berger,[13] Parhon and Goldstein,[14] Westphal,[15] Raecke,[9] Ormerod,[16] Knoblauch,[17] Oppenheim,[18] Healy,[19] Pitres and Marchand,[20] Wechsler,[21] Arbusse,[22] and Langworthy and associates [23] indicate the traditional and difficult problem of differentiating multiple sclerosis with psychic disturbances from purely psychogenic disease with both psychic and neurological somatic symptoms.

Jelliffe [24] introduced an interesting speculation about the etiology of multiple sclerosis. He believed the disease could result from purely psychological causes and advocated "a study of unconscious factors in this disease," with the conviction that "there would be found, in certain types of the disease, certain vascular alterations which produce the plaques." There is little evidence to support this psychogenic theory of etiology. However, Putnam [25] has suggested that the damage to the nerve tissue in multiple sclerosis is secondary to the clotting of blood in the cerebral venules. He postulated that various stimuli, such as infections, pregnancy, or emotional upsets, effect changes in blood physiology, with an increased rate of blood coagulation. Langworthy [11] has reported cases of multiple sclerosis in which the onset and progress of symptoms were related to personality problems. With the qualification that his data are not necessarily applicable to all cases, Langworthy poses the question "whether vascular changes in the brain related to neurotic difficulties could lead, in turn, to organic changes."

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13. Berger, A.: Einè Statuistik über 206 Fälle von multipler Sklerose, Jahrb. Psychiat. u. Neurol. **25**:168-188, 1905.

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15. Westphal, E.: Multiple Sklerose und Hysterie, Deutsche med. Wchnschr. **32**:321-403, 1906.

16. Ormerod, J. A.: Two Cases of Disseminated Sclerosis with Autopsy Reports, Brain **30**:336-364, 1907.

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25. Putnam, T. J.: Studies in Multiple Sclerosis: Etiologic Factors in Multiple Sclerosis, Ann. Int. Med. **9**:854-863, 1936.

The role of the premorbid personality in determining the psychic disturbances in multiple sclerosis has been studied by Brown and Davis,[26] Sugar and Nadell,[27] and Langworthy and associates.[23] These authors conclude that the psychic manifestations in multiple sclerosis are dependent upon the patient's premorbid personality.

Historically, there has been a tendency to correlate the psychic symptoms of any organic neurological disease with the pathological lesions in the nerve tissue. Damage to the cerebral cortex has repeatedly been indicted as the cause of the psychic disturbances in multiple sclerosis, as evidenced by the reports of Valentine (1856), Lannois,[28] Geay,[29] Seiffer,[8] Raecke,[9] von Bechterew,[30] Redlich and von Economo,[31] Nonne,[32] Boettiger,[33] and Brown and Davis.[34] The conclusions of Arbusse [22] and Langworthy and associates [23] are more tenable. These authors found it impossible to correlate the psychic disturbances in multiple sclerosis with any localized lesions in the nervous system.

An interesting aspect of the differential diagnosis of multiple sclerosis is its frequent confusion with dementia paralytica. The pitfalls encountered in making this differential diagnosis have been stressed by Schultze,[35] von Bechterew,[30] Lannois,[28], Kaplan,[36] Geay,[29] Seiffer,[8] Spiller and Camp,[37] Knoblauch,[17] Oppenheim,[18] Raymond and Touchard,[38] Boettiger,[33] Dercum,[39] Bassoe,[40] Wechsler,[21] and Arbusse.[22] Seiffer [8] pointed out that psychic disturbances in multiple sclerosis were no different from those seen not only in dementia paralytica, but also in senile, alcoholic, and arteriosclerotic psychoses.

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26. Brown, S., and Davis, T. K.: Multiple Sclerosis, Association for Research in Nervous and Mental Disease Monographs, New York, Paul B. Hoeber Company, 1921, pp. 76-82.

27. Sugar, C., and Nadell, R.: Mental Symptoms in Multiple Sclerosis: Study of 28 Cases with Review of Literature, J. Nerv. & Ment. Dis. **98**:267-277, 1943.

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40. Bassoe, P.: Report of a Case of Multiple Sclerosis with a Delusional State and Terminal Delirium, J. Nerv. & Ment. Dis. **45**:268-269, 1917

REPORT OF CASES

CASE 1.—A white man aged 53, a dentist, the youngest of five male siblings, first showed signs of multiple sclerosis at the age of 28. The patient's father died of unknown cause when the patient was 13 months of age. One brother died at the age of 42, after having been unable to walk for several years because of an illness which the patient claimed was not multiple sclerosis. The parents wanted a girl when the patient was born, and he wore dresses and long hair until he was 3 years old. He was always his mother's favorite, and after the death of the father the older siblings were required to care for the patient. His early childhood is described as being not unusual and as free of significant neurotic traits. After graduation from high school, at the age of 18, he worked for two years and then entered dental school. He was graduated from the latter with high grades and was considered a popular student with both faculty and students. He practiced his profession successfully, was happily married, and did not show definite symptoms of his illness until the age of 28. Over a period of several days vision decreased in his right eye to 20/200, with choked disk. Prior to the onset of definite symptoms of multiple sclerosis, and in retrospect, the patient recalled that at the age of 21 he noted subnormal distant vision and that at the age of 22 he had a sudden deafness of the right ear, after several days of ringing in that ear. When he was 34, he was noted to be subject to periods either of mild euphoria, with excessive energy and activity, or of quietness, during which he was less sociable and seemed moody and preoccupied. About the same time he experienced vertigo and syncope intermittently. By the time he was 36 he was reported to be "nervous," and to suffer from severe headaches and insomnia. At this time he was examined at the Mayo Clinic, and the following pertinent findings were noted: Vision was 6/12 in the right eye and 6/6 in the left eye. Funduscopy revealed partial simple optic nerve atrophy of the right eye with mild blurring of the disk margins. Right divergent strabismus was present. Repeated perimetric measurements revealed a central scotoma in the right eye. There were a conduction type of deafness in the right ear; slight horizontal nystagmus; increased deep reflexes on the right except for the Achilles reflex, which was reduced; equivocal plantar reflex on the left of extensor type; tremor of the hands; slight incoordination of the upper extremities, and ataxia. Examination of the spinal fluid revealed a negative reaction in the flocculation test and a colloidal gold curve of 0000111000. The diagnosis was retrobulbar neuritis, possibly due to multiple sclerosis.

Five years later, and at the age of 41, he began neglecting his dental practice. He spoke with a pressure of speech, with gradual appearance of evidences of delusional thinking. On one occasion he locked all the windows and doors, fearing that someone was trying to harm him. According to his wife, the patient's mother was visiting him at this time, and there was much discord among the three of them. The wife believed that this discord precipitated the patient's psychotic state. The patient was hospitalized for an undetermined period because of his psychotic symptoms, which apparently remitted spontaneously. Two years later, and at the age of 43, he attempted to return to his practice but had to give it up because of poor motor coordination. His wife stated that at that time he showed no evidence of mental disturbance and was "good-natured and sociable."

The patient was practically bedridden by the age of 47 because of weakness of the left side. His voice was harsh and strained, and he began to have crying spells without any associated feeling of sadness. Incoordination became so severe on the right side that he could no longer feed himself. In spite of his disability, he stated that he felt fine; he had an excellent appetite, slept well, and had no pain. The patient was admitted to the Veterans Administration Hospital, Topeka, Kan., when he was 50 because of the increasing difficulty in giving him adequate nursing care at home. Examination revealed a cheerful, friendly, cooperative, nonambulatory patient, who had to be fed because of the marked incoordination of the right arm. Neurological examination revealed pronounced pallor of the temporal half of the right optic disk; complete loss of internal and upward rotation of the right eye, so that it was fixed in a position of extreme external rotation; bilateral exophthalmos, more pronounced on the right; weakness of the left facial muscles; nerve deafness on the right; abnormal speech with a harsh quality and of explosive character; complete left hemiplegia with moderate muscular atrophy, as well as moderate contracture in flexion of the arm and extensor rigidity of the leg; marked incoordination of the right extremities with overshooting of the mark in intentional movements;

normal light touch, pinprick and position senses but diminished vibratory sensation in the entire left leg and almost complete absence in the right leg; absence of the right biceps and triceps reflexes and the left biceps reflex; hyperactive left triceps reflex; normal patellar reflexes and moderately active ankle reflexes; a Babinski sign on the left, and absence of abdominal and cremasteric reflexes. Examination of the spinal fluid revealed 70 mg. of total protein per 100 cc. and a colloidal gold curve of 5555432100, with no cells and a negative Wassermann reaction. An electroencephalogram was reported as being normal.

Psychiatric examination revealed the patient's verbalizations to be coherent, concise, and to the point. At times he mispronounced words but seemed unaware of this. He was alert and fully orientated. There was no fixed trend of thought content. The patient was sociable and entered into discussions initiated by the examiner. Remote memory for details was deficient. He avoided mentioning his earlier hospitalization for mental illness, but when the subject was mentioned to him, he admitted it but tended to minimize its seriousness. He denied any period of depression and stated that he was unaware that he had at other periods been overactive, perseverative, and euphoric. The examiner was unable to elicit any evidence of delusional thinking at the time of the examination. His intelligence appeared to be above average, and his general fund of knowledge was in keeping with his education and experience. His judgment was not grossly impaired. His indifference to his physical status was in striking contrast to the degree of his disability. He was emphatic at all times that he "felt swell" and his facial expression was in harmony with this verbalization of mood. On occasions he had episodes, lasting a few seconds, during which his face became twisted into an expression of weeping, with tearing. He admitted awareness of these episodes but could not explain them, stating that he in no way felt sad or depressed.

Case 2.—A Negro aged 30 first exhibited symptoms of multiple sclerosis at the age of 26. He was an active, care-free child who completed the 10th grade at the age of 15, with no failures. Because of difficulty in finding a job, he enlisted in the Army in 1940 and later married a girl, with whom he lived for two years prior to his going overseas but from whom he has not heard since. In 1941 he was examined for a penile lesion, which was found to be nonvenereal. At that time he was found to be in good health, and his vision was recorded as 20/20 in each eye. In the summer of 1942 he took quinine for frequent attacks of chills and fever and at the same time experienced intermittent pain and dimness of vision in the right eye. After four such attacks during a period of two months, he experienced, within 24 hours in September, 1942, loss of vision in both eyes except for perception of light. The loss of vision was associated with photophobia and severe headaches. Vision returned in the right eye after four days and has remained unchanged, but vision in the left eye has never improved. In November, 1942, vision was reported to be 20/30 in the right eye and 1/200 in the left eye. The disks appeared pale, the left being paler than the right. No other physical abnormalities were noted. The patient was ambulatory and did not appear ill or in any discomfort. Examination of the spinal fluid, on Nov. 17, 1942, revealed a negative Wassermann reaction and a flat colloidal gold curve, with no globulin. On April 5, 1943, the patient became deluded in the belief that other patients were talking about him and that the ward attendants were sticking needles into him and were thus going to cut off his breath. In addition, loss of appetite, with the frequent vomiting of clear fluid and hiccups, was noted at this time. The patient remained quiet, cooperative, and seclusive. A nurse's note on Aug. 17, 1943, reported: "Has delusions of paralysis. He formerly worked laboriously but has lapsed into feigned paralysis since being knocked off his feet by a patient." Examination in August, 1943, revealed no physical and neurological abnormality other than the diminished vision. At that time the patient was described as quiet, seclusive, listless, indifferent, mute, and negativistic, with peculiar "Napoleonic" posturing, waxy flexibility, and jerky, manneristic gait. The diagnosis on his Army medical discharge was dementia praecox, catatonic type.

In March, 1944, it was reported that he was unable to use his arms and hands to feed himself or to smoke, and his legs seemed to be stiff and functionless. At times he was incontinent. He spent his entire time in bed or in a chair and made no effort to occupy himself. During waking hours he made movements with his hands over his abdomen, as though massaging it, and complained of constant pain. Examination at this time revealed auditory

hallucinations and emotional apathy, but the patient was oriented and memory seemed intact. In addition to the loss of vision first noted, the following neurological signs were noted: marked tremor of the hands; absence of the abdominal and cremasteric reflexes; hyperactive patellar and Achilles reflexes; bilateral ankle clonus; impaired position sense in the lower extremities, and impaired vibratory sense in the upper and right lower extremities. On July 20, 1944, an examination of the spinal fluid revealed a negative Wassermann reaction and a colloidal gold curve of 1233210000. During August and September, 1944, the patient received 14 electroconvulsive treatments, with 11 grand mal convulsions. It was noted that during the convulsions there was no movement of the lower extremities.

The patient was admitted to the Veterans Administration Hospital, Topeka, in 1947, and the following neurological signs were noted: The patient could detect only light and gross movement with the left eye; vision in the right eye was 4/100; crude testing revealed a large central scotoma of the left eye and a smaller central scotoma of the right eye; both optic disks were white and sharply demarcated; slight external strabismus was present in the left eye; convergence of both eyes was inadequate; the pupils were sluggish; the patient walked with his trunk flexed at a 50- to 70-degree angle and used a cane with the right hand, pressing his left hand against the left side of his chest; his gait was hesitant and uncertain, with slow, short, stiff, shuffling movements of the legs; there was mild generalized weakness of all extremities; the left arm could not be abducted at the shoulder joint more than 80 degrees; the left elbow could be straightened passively, but the arm could not be abducted more than 110 degrees at the shoulder joint; there was mild spasticity of all muscles of the extremities; marked thoracic scoliosis to the right and moderate thoracic kyphosis, absence of vibratory sense in both lower extremities, marked impairment of position sense in the lower extremities, moderately hyperactive deep reflexes of the upper extremities, extremely hyperactive deep reflexes of the lower extremities, absence of cremasteric and abdominal reflexes, a sustained left ankle clonus, and a Babinski sign on the left and an inconstant Babinski sign on the right. The findings in routine laboratory studies were within normal limits. Psychiatric examination revealed an apathetic patient, whose usually unconcerned facial expression was broken only by roaming glances toward the ceiling or pained facial contortions. During the latter he did not admit having any pain. His only spontaneous remarks were inquiries as to when he could go home, but he answered questions directly and and coherently. He attempted to cooperate fully, but at times seemed to lack perseverance and ability to follow directions. He was alert, and his memory was not grossly impaired. He admitted previous hallucinatory experiences, stating that they were relieved by the electroconvulsive treatments. In describing his condition, the patient stated: "Something has got control of me, but I heard it's radium. It keeps me awfully hot and smothering—a burning inside; so sometimes I can hardly breathe or talk." At times he experienced pullings on his body in all directions. He believed that his condition was due to ingesting radium in his coffee during one of his hospitalizations. He was oriented, and his general fund of knowledge was commensurate with his education and experience. Judgment was impaired. In the ward he sat alone, often moving his lips silently or pursing them and blowing out. He denied any hallucinations or that the lip pursing was in response to hallucinatory experiences. He conversed little with other patients, although he knew their names and felt that they were friendly toward him. He cooperated in all activities prescribed for him and expressed particular interest in his work in the art shop.

CASE 3.—A farmer aged 50 became incapacitated by multiple sclerosis at the age of 41. He was the seventh of eight siblings and had an unhappy childhood. His mother died of unknown cause when he was 2 years of age. During childhood he frequently wanted for the necessities of life and was often punished severely by his father and older siblings. He completed approximately the third grade of school. At the age of 10 he ran away from home and became an itinerant farm laborer. In 1918 he married a woman who owned a farm, and this marriage resulted in three children. During World War I he served in a labor battalion and thereafter worked as a farmer until he was disabled by his illness. In his farm community he was respected, and he had many friends.

In 1919 the patient noted weakness of his left leg. This cleared but recurred intermittently until 1938, when both his legs became weak, and he could not walk without a cane. He suffered recurrent dizzy spells, and his gait was unsteady for many years, so that he

frequently had the sensation of "being drunk." In 1939 the diagnosis of hysteria was made. Because of urinary incontinence, transient blindness, vertigo, motor incoordination, and weakness, he was hospitalized in 1941 and has been in the hospital continuously since.

Neurological examination at the Veterans Administration Hospital in Topeka revealed the following pertinent signs: constriction of the peripheral visual fields; incoordination of the arms; spastic paralysis of both legs; diminution of pain and touch sensation over the face and of all modalities of sensation in the lower extremities; bilateral astereognosis; bilateral hyperactive patellar reflex; bilateral Hoffmann and Babinski signs, and urinary incontinence. The findings in routine laboratory studies were within normal limits. Examination of the spinal fluid revealed a trace of globulin; 50 mg. of total protein per 100 cc., a negative Wassermann reaction and a colloidal gold curve of 4443210000.

Psychiatric examination revealed the patient to be quiet and untidy. His speech was slurred and scanning and almost unintelligible at times. He was cooperative and responded readily and relevantly to questions. He appeared to be alert and attentive. While he was unable to name the day, he was well oriented for place and person. His memory for recent events was poor; remote memory was defective. He denied having illusions, delusions, and hallucinations. His thought content revealed no unusual trends. He dreamed occasionally of being a vagabond and of traveling around the world, visiting buildings with tall steeples. He manifested a mild degree of euphoria; otherwise, his affect was undisturbed. There was little spontaneity and no impulsiveness. He was not easily influenced and was negativistic at times. He appeared to be of low-average intelligence. He developed good relationships with physicians, but associated little with other patients because of his unintelligible speech.

Case 4.—A white man aged 40, a carpenter, first showed signs of multiple sclerosis at about the age of 34. The patient was one of eight siblings, born of parents of average financial means. He described his childhood as a happy one. It is reported that he was an active child who had many friends and enjoyed his school work. He was graduated from high school with average marks and then learned the trade of carpentry. He was happily married, with two children, and served for 15 months in the Navy, being honorably discharged on points.

At the age of 34 the patient first noted that his speech had changed. Since that time his speech had become increasingly slurred. Three years prior to admission he started veering to the left when walking and had to avoid running into people. There was some progression of his symptoms during the last month of his naval service, but was not incapacitating enough for him to report to sick call. Shortly after his discharge from the service, he noted progressive muscular weakness, more pronounced in the lower extremities, and at the same time his gait became more ataxic. Motor incoordination, tremor of the lower extremities, slurred speech, and muscular weakness increased to the point that he was unable to work at his trade, and he was hospitalized at the Veterans Administration Hospital in Topeka.

Neurological examination revealed the following significant signs: horizontal and vertical nystagmus; slurred, scanning speech; muscular weakness in the lower extremities; coarse tremor in the lower extremities; ataxia, with a tendency to fall to the left; diminished vibratory sense in the lower extremities; hyperactivity of all deep reflexes, and absence of abdominal and cremasteric reflexes bilaterally. The findings in routine laboratory examinations were within normal limits. Examination of the spinal fluid revealed 51 mg. of total protein per 100 cc., negative Wassermann reaction, and a colloidal gold curve of 1122210000. A roentgenogram of the skull and an electroencephalogram were reported as showing nothing abnormal.

Psychiatric examination revealed the patient to be alert and oriented in all spheres. There was no impairment of his recent memory. His thought content showed preoccupation with his failure to hold a steady job and the resulting financial worries. He discussed his symptoms frankly and revealed an attitude of resignation to them. His remote memory showed no impairment. There were no delusions or obsessions. His intelligence was estimated to be below average and his knowledge commensurate with his experience and education. His judgment was considered to be good, and he had some insight into his condition. Affect was not always appropriate. His appearance was that of sadness, and several times he cried during the examination, but stated that he did not feel unhappy on such occasions. A tendency toward euphoria was noted. The patient was active in occupational and recreational

therapeutic activities and was usually busy doing something around the hospital. He made friends easily with the other patients and seemed to be liked by them. He slept without sedation.

COMMENT

There are many reports on the psychic disturbances observed in multiple sclerosis, but psychosomatic studies based on a dynamic holistic concept of personality are few. The publications of Brown and Davis [26]; Arbusse [22]; Langworthy, Kolb and Androp,[23] and Sugar and Nadell [27] are pertinent, as these authors have indicated that the psychic disturbances in multiple sclerosis are dependent upon the premorbid personality. Jelliffe,[24] Putnam,[25] and Langworthy [11] postulated that emotional disturbances can give rise to the somatic symptoms of multiple sclerosis, probably through the medium of circulatory impairment. These causative emotional disturbances should be considered as intrinsic components in the pathogenesis of multiple sclerosis.

On the basis of the holistic principles expressed in our introductory paragraphs, it is our belief that the psychic symptoms in multiple sclerosis may be expressions of a lower-level reintegration of personality within the environment. If the postulated psychogenicity of somatic symptoms in multiple sclerosis is tenable, one must also consider the possibility of psychic symptoms that are expressions of personality reintegration having a psychogenic role, in turn, with the potentiality of giving rise to further somatic symptoms.

Hollos and Ferenczi [7] presented a psychoanalytic concept based on the dynamics of regression to explain the psychotic disturbances in dementia paralytica. We have suggested that regression and the process of disintegration-reintegration described by Teitelbaum [6] are related phenomena, occurring on psychological and physiological levels, respectively. Either system of dynamics can be applied to the study of psychic disturbances in multiple sclerosis, as well as other organic diseases of the brain. In a slowly developing brain disease one might have "a simple deteriorative process," according to Hollos and Ferenczi,[7] for "the traumatic factor is lacking, which can lead to the mobilization of great quantities of narcissistic libido, and provoke a paretic melancholia and mania."

Of the four cases presented, psychotic behavior was manifested in the first two. The first patient appeared to have a rather stable and well-integrated premorbid personality. In the history available there was no evidence of significant personality deviations prior to the onset of somatic signs of multiple sclerosis. Personality changes in the form of mood swings were in evidence 6 years later, but only after 13 years of illness did there occur a significant disintegration and lower-level reintegration or regression of personality, with deterioration of habits, failure to accept responsibility, and delusional loss of contact with reality. The patient's subsequent recovery from his psychosis is probably the result of a reintegration of personality on a higher level. This reintegration was most likely dependent upon his comparatively well-integrated premorbid personality. The patient may have achieved adequate narcissistic gratification during a period of hospitalization to lead to ego strengthening sufficient to allow him to give up his regressive escape from reality. However, there remained deviations from his original personality structure, evidenced by euphoria, denial of his disabilities, and amnesia for the psychotic episode.

Case 2 presents an interesting sequence of events that challenged precise diagnosis for about two years after the onset of the patient's illness. In retrospect, it

was apparent that an early loss of vision was the first sign of multiple sclerosis, a not uncommon initial symptom in this disease. The development of a frank psychosis, diagnosed as schizophrenia, before the appearance of additional somatic symptoms of multiple sclerosis indicates how intrinsically the psychic disturbances in this disease are a part of the total clinical picture. Although the failure of electrically produced convulsions to involve his legs indicated the spinal nature of the patient's paraplegia, the inadequate, but established, diagnosis of schizophrenia apparently prevented the observers from interpreting this phenomenon correctly, and the correct diagnosis was not made until a year later.

Rather than attempt to analyze the probable dynamics of regression in this case, as has been done in Case 1, we should like to point out a nosological problem made evident by Case 2. Certainly, the diagnosis of schizophrenia was incorrect and inadequate. A descriptive nosological classification of this patient's total disease, using conventional systems, leaves much to be wished for. In fact, the term multiple sclerosis does not connotate the complex personality disturbance observed in patients like this one.

Case 3 is included as an instance of a patient with an unstable premorbid personality who failed to manifest any psychotic behavior despite disabling multiple sclerosis. This case also is one in which an erroneous early diagnosis of hysteria was made. One might ask whether the discrepancy between this patient's early instability and the absence of any overt psychotic reaction is evidence of the inadequacy of the theoretical principles applied to Case 1. Case 3, we believe, demonstrates that the complexity of personality dynamics is so great that a much more detailed and careful study of individual patients is indicated if the problem of psychic disturbances in organic brain disease is to be understood. Goldstein [1] has stressed this need in his study of brain injuries. Case 4 is included to illustrate premorbid stability associated with well-retained personality structure in the presence of multiple sclerosis.

SUMMARY

The dynamics of the holistic concept of personality as an organism-environment system has been elaborated by Teitelbaum [6] as an integrative process of the cerebral cortex. In traumatic situations, either psychogenic or organic, the normal cortical integrative processes may undergo disintegration and reintegration on a lower level, with a more limited range of adjustment of the organism within its environment. The process of cortical disintegration and reintegration is considered as the physiological phase of the mechanism, of which the psychoanalytic process of regression is the psychological phase.

The previous literature is reviewed to show how the various problems related to the psychosomatic aspects of multiple sclerosis have been considered in the past.

Four cases of multiple sclerosis are presented, and their psychosomatic aspects are discussed in the light of the dynamics referred to above.

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Special Article

EXPANDING CONCEPTS IN NEUROPHYSIOLOGY

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IN 1748 Albrecht von Haller, the Swiss physiologist and physician, found himself the unwilling recipient of the dedication of an anonymous pamphlet entitled "L'homme machine." [1] Nothing could have been more at variance with his pious philosophy, and the controversies aroused by its theme burned with a white heat.

The message carried by this pamphlet, which was almost certainly written by the French physician, La Mettrie, was that man's sole guide to the universe is the observations he makes and that preconceived deductions are valueless. Nearly two centuries later Einstein gives us the same warning against metaphysics: "In order that thinking might not degenerate into 'metaphysics' or into empty talk, it is only necessary that enough propositions of the conceptual system be firmly enough connected with sensory experiences."

The author of "L'homme machine" expresses himself in terms which for his century are strongly neurophysiological. The "faculties of the soul" are held to depend on "the proper organization of the brain," for, he says, "so far then am I from thinking that thought is inconsistent with organized matter, that I look upon it to be a property as much belonging thereto as electricity, impenetrability, extension etc."

In spite of semantic difficulties with the word *esprit* (the French language having no exact equivalent for "mind") and in spite of the author's innocence of what Galvani, Lavoisier, Darwin, and Cajal were later to reveal, anyone who has followed the recent developments in neurophysiology cannot fail to hear the echo of this voice from the 18th century.

One is reminded of it when reading a paper which appeared in 1947, nearly 200 years later, entitled "How We Know Universals: The Perception of Auditory and Visual Forms," by Pitts and McCulloch.[2] This paper is the logical development of

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"If we have any insight into mind, or any eye for human history, we must confess at the same time that the oracular substitutes for knowledge to which, in our perplexities, we might be tempted to fly, are pathetic popular fables, having no other sanctity than that which they borrow from the natural impulses they play upon. To live by science requires intelligence and faith, but not to live by its folly."—Santayana.

1. L'homme machine, anonymously published, 1748.

2. Pitts, W., and McCulloch, W. S.: How We Know Universals: The Perception of Auditory and Visual Forms, Bull. Math. Biophys. **9**:127-147, 1947.

some earlier work evolving a mapping of nerve nets which, by virtue of reverberating circuits and branching connections, would determine the order of choice between incompatibles. The choice between ends was thus put on a possible neuronal basis.

In the 1947 paper designs are presented for neuronal nets based on known neuroanatomical structure which could furnish a basis for recognition of universal form when a particular specific stimulus arrives over sensory pathways. Here for the first time is a suggested mechanism for a neuronal apparatus by which the organism may know universals and respond to symbols of these universals, rather than to mere particulars. It is by the introduction of scanning circuits into the postulated network that these workers have been able to formulate a system by which impulses (which are particulars) arriving in any sensory nerve, at any moment in time, may evoke, not merely the reflex response to that particular, but the universal of which it is a part. One example is the recognition of chords regardless of pitch. The network they present, and for which they have computed the mathematical analysis, is based on the cytoarchitecture of the auditory cortex. Another example is the recognition of shape regardless of size. This is an ability shared in some degree by animals lower than man; rats, for example, can learn to differentiate a square from a triangle regardless of the actual size.

The line of argument develops from the concept of reverberation in chains of neurones as a basis of recognition of universals. A neural mechanism involving a net into which impulses can enter and persist through time, to influence a response at a later date, is a comparatively new concept. The traditional theories of neuronal paths passing into, through, and out from the nervous system by noncircular connections provided no mechanism for retention of impulses; the signal passed through and perished. A self-reexciting loop of neurones, sharing neurones with other loops, in which reverberation can be set up by the entry of afferent impulses from different sense receptors gives and preserves the association between different particular events and allows the recognition of a universal to be sparked by the receipt of a particular. The first taste of the *madeleine* dipped in tea was sufficient to evoke in Proust the full setting of his lost childhood happiness. The sight of a bird, whatever its shape, size, color, or orientation, the written or spoken word for it in any of the languages known to us, the sound of its song, the feel of its wings in the dark, and sometimes even its smell, will inform us of the same universal.

The uniformity of the nerve impulse, the unique form of the nerve action potential, makes possible this blend of stimuli, specificity having been left behind at the receptors. The number of neurones in the human brain, approximately 10,000 million, is sufficient for a vast number of intercommunicating nerve nets.

Man has a far greater ability than animals to extract the factors common to many different sense impressions received at different times and to synthesize them into a universal. Köhler's apes could, however, achieve a combination of two, and sometimes more, experiences occurring in isolation and at different instants in time, and not related in time as are conditional reflexes. There must, in these apes, have been some retention of components of each separately occurring experience and an integration of them, which they later used. Where could be the nets in which these essentials are retained and integrated? Are they perhaps in the cortical association neurones, Parker's "internuncial apparatus," which has twice as great a mass in

man as in ape? Where man is alone in his achievement is in the construction of symbols by extraction from his experiences and the use of these later for semantic formulation, such as language, or the symbols of logic or mathematics.

Not only does the new orientation towards neurophysiological mechanisms suggest (and this is the first time it has been done) a neuronal basis for choice and for the knowledge of universals; it also implies a mechanism for purposive behavior. The postulation of feed-back mechanisms introduces the possibility not only of self-regulating processes (with which physiologists are familiar) but also of self-directing systems. That such a system may have a neuronal structure brings goal seeking out of the clouds and into the nervous system. The first move in this direction was made in a paper published in 1943 by Rosenblueth, Wiener, and Bigelow [3] entitled "Behavior, Purpose and Teleology." Here, and again for the first time, a possible neural mechanism has been suggested for purposeful activity, by which signals from the goal can alter the behavior, by negative feedback, after it has been initiated and alter it in such a way that it may succeed in reaching the goal.

It is clear, as Judson Herrick has pointed out, that simple reflexes are not the elementary units of behavior and that the "actual conduct of animal and human bodies is not fabricated by monumentally piling up of simple reflexes."

A glance at the concepts referred to on the last few pages reveals how profound a change has taken place in neurophysiology, not only in the 200 years since La Mettrie, but in the last 25 years. This change in concepts of the nervous system is so great that it is almost impossible to overestimate it. In brief, it is a change from the concept of a passive, static nervous system to an active dynamic one. In the old concept the nervous system was bound in space by the paths of neurones, in direction by the Bell-Magendie law, and bound in time by the conduction rate of nerve fibers and the delay time at synapses. No persistence in time was possible, and the dimensions of its activity were rigorously imposed by the all-or-nothing law. It was temporally and spatially fettered.

The new neurophysiology has broken the fetters of this concept. Temporal summation, spatial summation, inhibition, all release the synapse from rigidity of response. After-potentials, after-discharge, and reverberating circuits release the nervous system from the fetters of time. No longer is the nervous system seen as responding only when it is stimulated. It can seize and retain stimuli and respond to them at a later time. One no longer seeks merely an individual response to the individual stimulus; it can respond to the category. And now it has been emancipated in space by the discovery of moving fields of direct current potentials, making possible the use of other parts of the brain than those directly served by the specific incoming nerve pathway. An object seen with one eye is recognized with the other. A system learned through one sensory system is recognized by another. The tune that is read from the score can be recognized by the ear.

All this is consistent with the central nervous system being not a mere relay station, which, when unstimulated, is at rest, but a system which is in itself a hive of activity, clues to which can be found in the incessant electrical activity of all neurone aggregates both in the cord and in the brain. The literature of the latter (electroencephalography) is vast.

3. Rosenblueth, A.; Wiener, N., and Bigelow, J.: Behavior, Purpose and Teleology, Philos. Sc. **10**:18-24, 1943.

These new concepts, these new hypotheses of neural mechanisms serving choice, the recognition of universals and purposive behavior, call for an architectonic design involving scanning circuits, reverberating networks, and pathways for feedback, and the neurophysiologist who wants to test these hypotheses is now faced with a search for the anatomical and histological existence of such circuits and for physiological evidence of their functioning in this way.

It is not very widely realized that in fact the existence of examples of this kind of circuit in the central nervous system were discovered histologically before man's reasoning had demanded such structures to account for his observations. On April 28, 1903, the greatest of all microanatomists of the nervous system, Ramón y Cajal, professor of histology at Madrid, addressed the conference of the Faculty of Medicine on the structure of the optic thalamus.[4] He described to his audience some remarkable findings in the lateral geniculate bodies of the cat, the mouse, and the human infant. There he had found two kinds of cells—some small with short axons and many dendrites, others large and star-shaped with long axons traveling to the optic cortex in the calcarine fissure, where he could demonstrate their arborizations around cells of the granular layer. Moreover, the axons of these same star-shaped cells gave off collaterals before they left the geniculate body, these collaterals remaining entirely intrathalamic. But he also found corticothalamic axons running down from the cells of the optic cortex to terminate freely in discrete islands in the lateral geniculate body with arborizations surrounding and enclosing the cells with short axons. These, in turn, arborized with the ascending thalamocortical neurones, thus forming a loop.

Since there is field-to-field representation from the retina to the lateral geniculate body, why, asked Cajal, should some islands of cells in this way station be so exclusively served by returning axons from the optic cortex? And what was the function of the cells with short axons? He suggested three possible functions for the structural arrangement he found. One (*hipótesis de la acción espectante*) was that impulses from the whole visual field would initially reach the geniculate body and beyond it to the cortex, where the returning corticothalamic neurones would convey impulses back only to these specific islands of the geniculate body and there facilitate transmission at those cells with which they arborized. Such a mechanism would enhance the sensation from a particular section of the visual field, which would then receive the observer's especial attention.

Cajal's second hypothesis (*hipótesis de la inhibicion*) was similar but reversed, namely, that these corticothalamic impulses exert an inhibitory action on the cells around which they terminated, allowing attention to be given to that part of the visual field whose connections in the lateral geniculate body did not receive them. Both these suggestions anticipated the introduction into neurophysiology of the engineer's concept of feedback.

It is in his third hypothesis (*hipótesis del refuerzo nervioso*) that one hears even more clearly the ring of future postulates. He suggested that there may be some "stored" activity persisting in neurones of the thalamic centers which enables weak impulses in the primary sensory pathways to be reinforced and so reach the cortex and evoke the phenomenon of perception. It is to the many neurones with short axons which he found in the thalamic centers that he allotted this function of accu-

4. Ramón y Cajal, S.: Plan de estructura del talamo optico, Semana méd. **10**:854-860, 1903.

mulated activity, which, had the hypothesis been formulated today, would probably have been named "reverberation." Here is the concept of impulses in a net persisting through time to influence a response at a later date.

The neurophysiologist has still a long way to travel in his search for more of these structures in the central nervous system, and, having found them, has an even harder task in demonstrating that impulses do indeed circulate within them. It is perhaps well to bear in mind Cajal's final warning that his explanations of these mechanisms are *conjetura*.

Correspondence

CORRECTION IN OBITUARY OF DR. GEORGE B. HASSIN

To the Editor:—In the obituary which was published in the December, 1951, issue of the ARCHIVES, there occurs (page 814) a statement beginning, "When it was rudely and unnecessarily taken from him, . . ." The reading of his correspondence and the financial statements of the *Journal of Neuropathology and Experimental Neurology* have convinced me that this statement is erroneous. I retract it and apologize sincerely for its implications.

The facts are as follows:

1. The founders and supporters of the *Journal of Neuropathology and Experimental Neurology* were originally Dr. G. B. Hassin, Dr. J. H. Globus, and Dr. A. Ferraro. To this group Dr. Arthur Weil was later added.

2. On a previous occasion the late Dr. G. B. Hassin decided to take upon himself the transfer to Chicago of the executive office of the *Journal*, a move which did not materialize because of the strong opposition of the other founders.

3. The late Dr. G. B. Hassin unilaterally took steps to give the *Journal* to the University of Illinois. This move was also strenuously objected to by the other founders.

Because of this objection, the late Dr. G. B. Hassin decided to withdraw from his association with the *Journal of Neuropathology and Experimental Neurology* and from his position as editor-in-chief of the said journal.

His resignation as editor-in-chief and the severance of his connections with the journal were actuated by the late Dr. G. B. Hassin out of his own free will, and against the repeated individual and collective pleadings of the other founders of the journal that he remain connected with the journal and retain his position as editor-in-chief, without any financial obligation on his part.

PERCIVAL BAILEY, M.D., Chicago.

Society Transactions

CHICAGO NEUROLOGICAL SOCIETY

John Martin, M.D., President, in the Chair

Regular Meeting, Dec. 11, 1951

Preliminary Report on Hibicon.® Dr. Leo A. Kaplan and Dr. Stanley Maslanka.

Hibicon® (N-benzyl-β-chloropropionamide) is a new anticonvulsant developed in the laboratories of Lederle Laboratories Division. We began using the drug about two years ago in the free dispensary epilepsy clinic of Mercy Hospital.

A total of 31 patients with convulsive disorders were treated. All were considered to have refractory conditions and had received all the commonly known anticonvulsant drugs for many years, with poor control of their seizures. The conditions included idiopathic epilepsy and epilepsy of organic origin, such as post-traumatic states, cerebral vascular accidents, postoperative disturbances complicating brain tumors, and dementia paralytica.

The epileptic attacks were classified as grand mal, grand mal and petit mal, and psychomotor equivalents. There was no case of focal epilepsy, and only one case of psychomotor equivalent.

We arbitrarily established the following criteria for control. If the control of seizures was increased 50% or more above the rate with the former medication, the condition was considered as greatly improved; if 25 to 50%, as slightly improved, and if less than 25%, as not improved.

In the following tabulation are presented the results of treatment in all cases in this series regardless of the type of seizure activity or the cause.

Great improvement	16 (51+%)
Slight improvement	6 (19+%)
No improvement	9 (29+%)

A breakdown of the series according to the type of seizures regardless of the etiologic factor follows:

Effect	Grand Mal	Grand and Petit Mal	Psychomotor Equivalent
Great improvement	10 (47+%)	4 (44%)	1 (100%)
Slight improvement	5 (23+%)	4 (44%)	.....
No improvement	6 (28+%)	1 (11%)	.....

Lastly, the cases were classified on an etiologic basis.

	Idiopathic	Organic
Improvement	11 (64%)	9 (64%)
No improvement	6 (35%)	5 (35%)

No signs or symptoms of toxicity were observed. All the patients commented on their subjective improvement. No sedative effect was noted by any of the patients.

Some that failed or did poorly on hibicon® alone showed improvement when a combination of hibicon® and diphenylhydantoin was given.

We believe that the results justify the conclusion that hibicon® will be another useful drug in the armamentarium for the treatment of convulsive disorders.

DISCUSSION

Dr. A. Arieff: Over the past few years I have had experience with the use of hibicon® in 10 patients. I had followed all these patients from 10 to 15 years before hibicon® was used. With none of them was hibicon® given as the sole drug; rather, it was used with other anticonvulsant drugs. All these patients had psychomotor equivalent seizures in addition to attacks of grand mal or petit mal.

In 3 of 10 patients a remission of the attacks of psychomotor equivalents was produced. In one patient the remission lasted one year, and then the previous frequency of attacks was resumed. This rhythm follows the sequence of remissions and exacerbations with other drugs. The second patient had a remission for eight months and then had an exacerbation of psychomotor equivalent and grand mal seizures. The third patient had a remission of psychomotor equivalent attacks for five months, with continuation of this remission for three more months, only to have an exacerbation.

From these data, it is difficult for me to evaluate the efficacy of hibicon.® When one follows patients for many years, one finds that remissions may come for no apparent reason, to be followed by exacerbation for no apparent reason. With respect to the criteria of refractoriness, how long did Dr. Kaplan follow his patients personally? I believe that the criteria for evaluation of an anticonvulsant drug should be made more universal. Although it may be considered an improvement when the number of spells are cut down from five to two a month, it would not be a remission. A remission should be measurable only in years, or the drug is of no value.

It has been my custom to report the efficacy of an anticonvulsant drug only after it has produced a remission of all spells for at least six months to one year. I know that this report is a preliminary one, but if the results of treatment for the three patients illustrate the efficacy of the drug, I should say that hibicon® has little value.

DR. H. CHOR: What were the undesirable effects of the drug?

DR. LEO KAPLAN: The families commented on the well-being of these patients since they had been on hibicon.® The patients were more alert, more cooperative in the family. We encountered no gastrointestinal disturbances. We saw no evidence to indicate the necessity of thorough blood studies, which we did not make, although the Lederle Laboratories had made such studies before we received the drug. We had no cases of pure petit mal. All the patients had combinations of petit mal and grand mal, pyknolepsy, or psychomotor equivalents. Electroencephalographic studies were done only initially on these patients. After treatment with hibicon® we did not make an electroencephalogram. We were interested only in finding out whether the drug had anticonvulsant properties.

In answer to Dr. Arieff, I do not think that hibicon® is a panacea or cure for epilepsy, any more than the other drugs now in use, and I do not think that hibicon® is going to be any better than the drugs that are now in use. I believe that is has anticonvulsant properties. We have seen its effect in the past 20 months. As to the criteria for refractoriness, all these patients had been in the clinic for years, some as long as 15 to 20 years, and had received all the known anticonvulsants, and they had done very poorly. They came with a history of grand mal seizures every day, or several times a day, or of having petit mal seizures, 15 to 20 a day, and had been treated with the other known anticonvulsants. The cases that we cited were not primarily the ones in which results were the best.

I did not want to make this a tedious paper and did not include details that we can put in a published article. We followed the criteria used by others who have reported on anticonvulsant drugs. Our method was simple: If a patient had 50% reduction or better in his seizures over that under previous medication, we called that great improvement. On the other hand, if he had a reduction of seizures of from 25 to 50%, we classified it as only slight improvement. From 0 to 25% reduction was rated as no improvement. Certainly, the results indicate that a certain percentage of these patients are showing a greater control of their seizures with hibicon® than with other medicaments. When other drugs fail to control patients, I believe that hibicon® should be tried alone or in combination with other anticonvulsants. It is a safe, nontoxic drug, with no side-reactions, and, from our preliminary study, appears to possess anticonvulsant properties of such a degree as to make it an additional useful drug in the treatment of convulsive disorders.

Mechanical Effects of Brain Tumor. DR. J. W. KERNOHAN, Rochester, Minn.

When an intracranial tumor attains a sufficient size, it exerts a mechanical effect on the surrounding brain. Sometimes the results are evident in the immediate region, and sometimes at a considerable distance. Some phenomena produced by the displacement of the brain help in localizing the tumor, but some are, to say the least, confusing and entirely misleading. The

best example of which I am aware is the so-called crus syndrome, in which a tumor in the frontal, parietal, or temporal lobe of one hemisphere, for instance, the right hemisphere, displaces the brain stem toward the left side, so that the peduncle impinges on the free edge of the tentorium cerebri of the left side. This partially interrupts the pyramidal fibers coming from the left hemisphere. Tumors of the pituitary gland and some adamantinomas displace the optic nerves, optic chiasm, and anterior portion of the optic tracts upward, so that they are compressed by the anterior part of the circle of Willis. This compression produces a sharp groove in the visual pathway and interrupts the nerve fibers, thereby producing defects in the visual fields which are utilized in the localization of these tumors. Other effects of brain displacement will be demonstrated and discussed.

DISCUSSION

DR. PERCIVAL BAILEY: This is a remarkable series of photographs of these lesions. I noticed that Dr. Kernohan did not show any grooving of the lateral borders of the chiasm by enlargement of the carotid artery. I remember that Dr. Frazier believed that such lesions occur; personally, I have never seen a case. Dr. Kernohan did not show any. I wonder whether he has ever seen any.

Structural and Functional Regeneration in the Central Nervous System. DR. WILLIAM F. WINDLE, DR. C. D. CLEMENTE, DR. DONALD SCOTT JR., AND DR. W. W. CHAMBERS.

Our first report of anatomic regeneration in the transected spinal cord of cats and dogs was presented before a joint meeting of the Philadelphia Neurological Society and the New York Neurological Society, April 21, 1950 (A. M. A. ARCH. NEUROL. & PSYCHIAT. **63**:261 [Feb.] 1951). Since that time additional studies of cord regeneration have been carried out on about 80 cats. Other experiments, involving implantation of peripheral nerves into the brain, have provided information concerning the mechanism of inducing regeneration in the central nervous system.

In agreement with observations of most other investigators, we found no significant structural or functional regeneration occurring spontaneously in the surgically severed cord of adult cats. Anatomical regeneration as early as 30 days after operation occurred in at least 75% of animals in which therapy with a bacterial polysaccharide (pyromen®) was instituted at the time of transection. This therapy led to inhibition of glial scarring and proliferation of a loose matrix of reticular tissue at the site of transection. Sprouting neurons usually traversed the lesion along the processes of reticular cells. Electrophysiological studies demonstrated conduction in lateral columns across the site of transection. There appeared to be restitution of 12 to 25% of fibers stimulated in these tracts. Close approximation of the ends of the severed cord at operation was related to the degree of functional and structural recovery.

The central stump of the severed temporal branch of the facial nerve was implanted into the temporal cortex of cats. In controls the stump was isolated from the cortex by a quickly forming glial barrier. No such barrier formed in the cats receiving pyromen® therapy. Instead, the peripheral nerve fibers and the neurons of the cortex intermingled indistinguishably.

The results of the present experiments point unmistakably to the astrocyte barrier as the most important factor in preventing successful regeneration in the central nervous system.

DISCUSSION

DR. LESLIE W. FREEMAN, Indianapolis: My associates and I have now been working with this type of preparation for 4½ years. I might say that it is not common to have an animal show functional regeneration because of the difficulty in maintaining paraplegic animals for long periods. Adult animals present these difficulties of care to a much greater extent than younger ones. If, however, good health is maintained, those surviving beyond several months do show a high percentage of functional regeneration.

(A slide was presented illustrating the growing neurons with their end-bulbs in the distal stump of the divided spinal cord of a rat.)

The occurrence of functional regeneration has been established on the following bases: (1) progression from a state in which the hind extremities are dragged with the forelimbs to good walking; (2) the animal's ability to climb up and down and to support itself on the hindlimbs

while brushing an irritating material from the face; (3) disappearance of these abilities upon retransection of the spinal cord, without abolition of the spasms of these limbs; (4) induction of a transient paraplegia injection of procaine into the site of previous transection which exists only for the duration of action of the drug, again without abolition of reflex activity, and (5) the proximal and distal stimulation of the spinal cord with observation and measurement of neuronal conduction.

In our experience, the introduction of any material between the divided ends of the spinal cord has led only to a greater amount of fibroblastic scarring. These scars are extremely dense, and very few fibers are seen to enter the region. In most of the better preparations, it appears that a longitudinal orientation of the scar has occurred, serving perhaps as a bridge for the growing neuron. Most of the fibers observed cannot be traced back to the spinal nerve roots. Indeed, the surgical technique is such that roots are not usually divided. Consequently, we believe that these fibers originate within the white matter and are truly of spinal origin. Functional regeneration with histological confirmation has been observed in the rat, cat, and dog. We have more success with young cats and dogs, perhaps because of the superior type of care given by the mothers.

The pyogenic material that we are using definitely reduces scarring and gives almost phenomenal results in incompletely divided spinal cords. For animals with complete transection, the survival rate is much greater among the treated animals. It is our feeling that Dr. Windle's discovery of the scar-prevention action of this drug will prove to be of great benefit in this field of study.

DR. PERCIVAL BAILEY: I am one of those who have encouraged work in this field. I have been one of the consultants of Paraplegia, Inc., since its beginning. This is the first encouraging report I have heard. I have no doubt, once the possibility of regeneration is established, that Dr. Windle will use better histological technique to bring out the details of these remarkable effects.

DR. W. F. WINDLE: I am delighted to have my friends and colleagues add their contributions to this discussion. We realize that there are many things to do in this field; we have further studies under way, and we hope to encourage other people to take up the work. We have no indications that pyromen* can bring about changes in the scar tissue of the brain or cord after that has become well formed. We are removing old scars in our animals to see whether regeneration can then be induced. We have done experiments in peripheral-nerve regeneration in rats but have no positive results as yet.

NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY, AND THE NEW YORK NEUROLOGICAL SOCIETY

H. Houston Merritt, M.D., *Chairman, Section of Neurology and Psychiatry, Presiding*

Joint Meeting, Nov. 13, 1951

The Meaning of Consciousness. DR. I. S. WECHSLER.

Consciousness is not a faculty or single entity but consists of a series of states of consciousness. It is the result of numerous integrations of simple and complex neural activities underlying mental processes. Consciousness is a relative concept expressive of a series of relationships. It is an attribute of integration, a function of the whole brain, including the autonomic nervous system.

Unconsciousness is a negative state. It ranges all the way from minor impairment to complete loss of consciousness; that is, there are many states of negative consciousness. As a psychologic concept the term unconsciousness is serviceable; as a neurophysiologic or neuroanatomic entity it has no validity.

Consciousness being a general function of the brain, it has no one seat. Therefore one cannot localize consciousness or states of consciousness. There are regions of less and greater integration, impairment of which will restrict or abolish consciousness.

Experimental or fortuitous impairment of consciousness, resulting, as it does, in negative states, at present contributes little to the elucidation of the ultimate nature of consciousness.

DISCUSSION

DR. SAMUEL BROCK: This provocative paper of my esteemed friend, Dr. Wechsler, is as difficult for me to discuss as it must have been for him to write. Consciousness involves so many facets of nervous activity, including the highly complex activity designated collectively as mental, that it does not lend itself to satisfactory study by present neurophysiologic techniques. Total awareness is made up of many cortical and infracortical functions blended in an ever-changing spectrum of variable activity, which can be analyzed only in a fractional study. Curiously, unconsciousness, the clinical "corresponding opposite," has a somewhat simpler pattern and can be more easily measured and assessed. Whether studies of unconscious states throw much, if any, light on the opposite, collective display of activity is a moot point. It might be said that no one studies consciousness as a global phenomenon, whereas many have pondered the problem of unconsciousness, largely because it is so often encountered in disease.

Unconsciousness is seen in one form or another, e. g., as sleep, as the hibernation of animals, as a reaction to drugs and toxins, as an effect of general brain injury, as a sequel to certain metabolic disturbances of the brain (cerebral anoxia), in certain cerebral vascular conditions (hemorrhage, syncope, carotid-sinus abnormalities), in cortical electrical disturbances clinically recognizable as petit mal, and as part of the grand mal attack. In some unusual conditions, viz., the cataplectic-narcoleptic syndrome, one encounters striking dissociations, in that the patient may become "motorially unconscious" and collapse, though mentally awake, or he may be subject to unusual periods of imperative sleep under conditions regarded as conducive to wakefulness. Similar dissociations are seen in the sleepwalker and the sleeptalker.

One is left with the thought that consciousness and unconsciousness are very basic biologic processes, in some ways comparable to life and death.

DR. EDWIN A. WEINSTEIN: The most important contribution is Dr. Wechsler's statement that consciousness in not an absolute modality but, rather, the expression of a relationship among elements. When he speaks of a disturbance of consciousness, he does not mean a "defect"; rather, he is thinking of a change in organization or pattern. Some such concept must be used in studying the phenomena observed in patients with disturbances of consciousness. Many neurologists, unfortunately, conceive of unconsciousness only in terms of sleepiness. Actually, a patient may be quite alert and show profound disturbances in his correspondence with the environment. Thus, persons with subarachnoid hemorrhage or tumors about the third ventricle, and persons who have had prefrontal lobotomy may be alert but disoriented for place and time, and may deny that they are ill in any way or have had an operation. These phenomena are not to be explained by loss of memory, topographic disorientation, or lack of judgment. Rather than a defect, there is a new perceptual-symbolic system of relationships between the organism and the various stimuli applied to it.

DR. ABRAHAM M. RABINER, Brooklyn: It is most unfortunate that for years we have had foisted on us this concept that functions must have areas of the nervous system assigned to them as centers. It is doubtful whether there are any such areas with a specific single function. There are areas where contiguity of bilateral cerebral pathways or cellular collections may be affected by a single lesion. Functions requiring normal activity of both cerebral hemispheres may then become impaired. Thus, we have been informed of centers in the midbrain and parasagittal region for sphincter control. These cannot be labeled centers, but are areas where bilateral corticospinal function may be affected by a single lesion.

Vital functions necessary for normal maintenance of the animal as a whole are not seriously disturbed by a lesion affecting one pathway or one collection of cells. There is no single lesion anywhere in the nervous system capable of causing unconsciousness. Consciousness may become impaired or lost when there is impaired conductivity of structures concerned with the passage of impulses from the environment through the sensorium to receptive areas in the brain. When a sufficient number of these structures are thus involved, there may be complete loss of consciousness, but variations may occur, ranging from partial unconsciousness to impaired consciousness for parts of the body structures.

DR. EDITH KLEMPERER: I should like to speak of only one factor, that is the dissociation of the various functions of consciousness in hypnosis. I take all my hypnoanalyses with a recorder. I play all these records back to the patient. Most of them remember the contents—some patients

better than others. But they do not always remember. The part which represents consciousness is sometimes rather fluctuating. I believe this dissociation is an interesting problem, if only a small part of the whole subject of consciousness.

DR. I. S. WECHSLER: I fear that Dr. Brock missed the most important point I tried to make. He concludes that "consciousness and unconsciousness have a variable neural basis." That is precisely what I said they do not have. Both are merely different aspects of the same function and have the same neural basis.

Dr. Rabiner's statement that there are no centers is too sweeping. If he means there are no completely independent centers, one may agree. Collections of ganglion cells may be looked upon as centers. There can be no center for such a great function as consciousness.

I did not discuss the psychology or philosophy of consciousness; I merely pointed out that unconsciousness, like consciousness, is a relative state, and that it cannot be equated with sleep. In every state of consciousness there may be lacunae of unconsciousness. This seems to me important for neuroanatomic and neurophysiologic thinking. If this point of view is accepted, there will be no longer the futile attempt on the part of neurosurgeons to localize consciousness in the striatum, in the hypothalamus or in various parts of the cortex. Some day we may learn what consciousness is. At present we do not even know neurophysiologically what an idea is. Scientists should not be beguiled by glib language. It is no secret that plausible writing can conceal some very bad thinking. Read metaphysics and what passes for philosophy and psychology.

I did not intend to discuss hypnosis; I merely mentioned it in passing. It so happened that I had occasion to study two or three cases of dual personality. The interesting point is that the patient appeared to be fully conscious in the primary and in the secondary personality and yet was totally unconscious of the one personality when he was in the other.

Drug Addiction in Adolescents. DR. PAUL ZIMMERING and DR. JAMES M. TOOLAN.

The present wave of drug addiction among adolescents was analyzed with reference to the admission rate for narcotic addicts under the age of 21 to the Psychiatric Division of Bellevue Hospital. During the first nine months of 1951, 301 adolescents and young adults were treated, as compared with 11 in 1950 and 1 in 1949. Some of the social and racial factors were discussed. The development of heroin (diacetylmorphine) addiction in adolescents was described. It is characterized by a progression from "snorting" to "skin popping" to (finally) "main-lining"; contraction of all interests, leading to truancy and renunciation of friends, family, and recreational and sexual activities; "hustling" at odd jobs, pawning of clothes and family effects, and petty stealing, and, finally, engaging in major criminal activities as a means of supporting the addiction.

Certain common characteristics were delineated in the group of addicts: 1. All but one were Negroes or of Puerto-Rican descent. 2. All were nonaggressive, verbally adept, socially graceful, and not typical delinquent boys. Their personal habits and preferences were conservative and subdued. 3. There was a sustained, close empathic relationship with a mother. The father was usually out of the picture because of death, separation, or lack of emotional rapport. 4. Object relationships in general appeared to be weak and tentative. They were readily given up under the influence of the addiction. 5. School and work inhibitions were very strong. 6. All had a similar subjective experiment under the drug, marked by euphoria, heightened self-esteem, fantasies of omnipotence, and withdrawal from social experiences that would challenge their self-evaluation.

The present wave of addiction among teen-agers involves a dynamic complex of determinants, including economic and social factors, but those with the characteristics enumerated are more likely to fall victims. These boys appear to have a problem in handling their aggressive drives. (The term "aggression" was used in a broad sense to describe active dealing with the environment, both destructive and constructive.)

DISCUSSION

DR. IRVING J. SANDS: Thirty years ago, when I was on the psychiatric service at Bellevue Hospital, we had a large number of drug addicts in our wards. At that time Dr. R. S. Copeland was Commissioner of Health, and he appointed a special deputy, the late Dr. Carlton Simon, to take care of the narcotic problem as it presented itself to the city. The police had then

"cracked down" on the peddlers, and Bellevue Hospital opened its dooors to any addict who needed treatment (Sands, I. J., and Blanchard, P.: Abnormal Behavior: Pitfalls of Our Minds, Moffat, Yard & Company, New York, 1923). The general picture of both the addiction and the type of addict has materially changed. There were relatively few Negroes then as patients, and the Puerto-Rican colony in New York was a negligible one at that time. The addicts then were above the adolescent age, and mostly white persons; and they contained a large number of elderly persons. After trying various means of treatment, we finally arrived at the method of "cold turkey." I have never seen any serious consequences of such method, except in a very few instances in which very old people responded with cardiac insufficiency. At that time the method of drug addiction was almost routine; the victim would begin with smoking opium, then take morphine and, eventually, heroin. At that time persons using heroin showed the most serious personality disintegration. Marihuana intoxication was unknown then. Today the problem is somewhat different. Most of the addicts are either Negroes or Peurto Ricans. I regard the drug-addiction problem as more sociological than medical. I believe physicians should recognize it, because members of the medical profession are going to be blamed for failure to solve the problem. It is said that there are not enough physicians, not enough clinics, and not enough institutions to treat the drug addicts. As a matter of fact, anyone who had dealings with drug addiction knows that very few drug addicts can be cured. It is very easy to take the addict off the drug, but as soon as he returns to his original neighborhood he goes right back to it. One must also remember that the drug addict who becomes a "mugger," or who carries a gun to obtain the drug, is a dangerous member of society and should be regarded as such. To cure drug addicts, it is imperative that one should get rid of the peddler. Of course, that does not mean that community centers, which could afford some sort of social outlet for underprivileged Negroes and the recent immigrants from Puerto Rico, should not be erected. However, the only method of solving the problem of drug addiction is by extermination of the seller (the "pusher" and the peddler), and this is a sociologic and social problem, rather than a medical one.

DR. EDWIN A. WEINSTEIN: I wonder whether the authors have any idea why these youngsters do not get withdrawal symptoms. Is it a matter of the length of time they have taken the drug? Second, do they have mixed addictions, particularly with alcohol or barbiturates? These types of addiction are very apt to give the type of aggressive behavior that heroin does not.

As to addiction being attributed to closeness to the mother, in the cultural milieu from which these patients come, it is the mother who keeps the family together, and the father is frequently an extra member. I wonder whether in a group of deprived children of similar background who were not drug addicts one might not find the same situation as applied to the mother.

DR. PAUL ZIMMERING: I agree with the first discussant that if there were no drugs there would be no drug addiction. I do not believe that if there were no drugs, these boys, who are disturbed boys, would necessarily resort to other types of antisocial or self-destructive behavior. However, it is important to note that in a certain neighborhood where drug addiction is prevalent, where the drug is pushed by peddlers, only certain types of boys will become drug addicts. Many more boys experiment with a drug, try it for a time, than those whom we see at Bellevue or those who actually become "hooked" by the drug. In essence, as we have studied this problem, we have not seen anything fundamentally different in the socioeconomic situation in some of these boys. Of course, our study is not a refined one. We also know boys who have broken themselves of the drug addiction. But a certain number of these boys just cannot break off, and the question is: Why can't they? We have interviewed boys who were so completely pessimistic about their ability to break themselves of the habit that they were desperate. They wanted to be sent away from home. This wish is extremely unusual on the part of a boy, for, no matter how bad the home situation is, he will cling to even a bad sort of parent and will want to be sent home. The most important thing in handling the problem is to deal with the socioeconomic factors and prevent the drug from getting to the boy, i. e., to do away with the traffic in the drug. Drug addiction is primarily a social problem and a police problem, but, being a psychiatrist, I was interested in the psychiatric factors.

The question of why these boys do not have severe withdrawal symptoms is one about which one can only speculate. They do not take large doses. The average boy takes the equivalent

of about a ½ grain (0.03 mg.) of morphine a day. They take from 1 or 2 to 20 capsules a day. Each capsule contains 1 to 2 mg. of pure diacetylmorphine. Another factor is that they have not been taking the drug over a long period. Possibly there are other factors—the physiology of adolescence, for example; but these two are the only possible explanations I can offer.

As to combined addiction: Some of the boys we talked to have combined heroin with marihuana. I do not think that any boys have combined heroin with alcohol. It is not a good combination; they do not particularly like it. Some boys feel that marihuana completely masks the effects of heroin, while others feel that heroin completely masks the effect of marihuana. The boys we see prefer heroin. We have also seen some boys who have taken heroin but preferred marihuana; they are not many, and the boys who preferred marihuana do not fit into our group, as we have defined the characteristics.

In our paper (Heroin Addiction in Adolescent Boys, *J. Nerv. & Ment. Dis.* **114**:19-34, 1951), we discussed our method of using a control group to test the validity of our observations on the mother-son relationship. Our conclusion was that "while the dominant position that the mother holds in the family may be typical for our culture, we had the impression in our group that her relative importance was overweighted."

Neoplasms Within the Midbrain. Dr. Martin G. Netsky and Dr. R. R. J. Strobos.

Four patients with neoplasms within and limited to the mesencephalon are presented and the necropsies reviewed. Early and prominent mental changes, including a wide range of disturbances, are common and are especially emphasized. These mental changes in combination with paralyses of conjugate gaze are commonest. Other neurologic signs frequently encountered are papilledema, ataxia, and pyramidal-tract signs. Of the diagnostic procedures, air studies are most revealing but are not infallible. The finding of an enlarged fourth ventricle does not exclude a neoplasm which partially blocks the aqueduct.

DISCUSSION

Dr. Samuel Brock: How does Dr. Netsky explain the dilated fourth ventricle?

Dr. Fritz Cramer: I should like to ask whether any of these so-called mental disturbances might be due to nonemotional reflexes or forced laughing and crying, rather than to true emotional disturbances.

Dr. Abraham M. Rabiner, Brooklyn: I should like to mention a patient at Montefiore Hospital in 1921. He had a mental disturbance, in addition to neurologic disorders, and autopsy revealed a neoplasm of the brain stem.

Dr. Martin G. Netsky: The mechanism of the dilatation of the fourth ventricle is a matter of speculation. A hypothetic explanation is that with distortion of the brain stem there is constriction of the foramina of Luschka and Magendie. The normal choroid plexus of the fourth ventricle continues to form fluid. In addition, the aqueduct may be partially patent, and there may be some porosity of the tumor. The emotional symptoms were not those of forced laughing and crying.

Spasmodic Torticollis: A Psychiatric Case Study. Dr. Harry Sterling, Brooklyn.

The psychiatric history of a white man aged 25 who had had spasmodic torticollis for the past three years was presented. The patient, referred by the New York Neurological Institute, had received psychotherapy for the past 1½ years. Material was presented to indicate that his faulty psychosexual development was closely related to his acquiring spasmodic torticollis, which was found to be only one of the many symptoms of his severe emotional illness. The main dynamic factors in his presenting symptom were (1) the displacement of head for penis, by which means he was able, unconsciously, to avoid real castration and also to gratify his many infantile autoerotic desires, mainly exhibitionism, and (2) the turning of his head, by which means he unconsciously made nonexistent, by not seeing, any danger he felt confronted by, at first incest and castration, and later any threat, particularly to his omnipotence. In the course of treatment, which he was still receiving at the time of the report, the patient had, for the first time, had periods of remission of his head symptom, although short and transitory.

DISCUSSION

DR. I. S. WECHSLER: What was the clinical diagnosis in this case?

DR. HARRY STERLING, Brooklyn: Pseudoneurotic schizophrenia. He has at no time exhibited any overt break with reality.

DR. IRVING J. SANDS: I wish to congratulate the author on an excellent presentation of the psychodynamics in a case of severe neurosis. I doubt, however, whether the patient had true spasmodic torticollis. The most difficult patients to treat are those with spasmodic torticollis, and it is rare that one really cures any patient with this disorder. In listening to the author, I had the impression that his patient was holding his head in that position as a defense mechanism against the gratification of certain instinctual urges which were unacceptable to his ego. I once had a similar case, that of a very intelligent, highly educated woman who was a nurse and presented, among her other symptoms, an inability to turn her head to the left. After many interviews, I learned that as a youngster she slept in a room next to her parents' bedroom, and that the door between these two rooms was invariably kept open. She would listen, with a good deal of anxiety, to what was taking place in her parents' bedroom. Her inability to look to the left was merely a defense mechanism to prevent her from reexperiencing her emotional reaction to these early infantile experiences. I think that the patient presented by Dr. Sterling is suffering from a severe neurosis, and I question the diagnosis of true spasmodic torticollis in this case.

DR. HAROLD G. WOLFF: May I ask for how long a period the patient had the position of his head altered as a result of the therapeutic efforts described?

DR. ABRAHAM M. RABINER, Brooklyn: I should like to enlarge a little on what Dr. Sands said. We have seen many patients with spasmodic torticollis who have been subjected to psychiatric treatment, and I, for one, have yet to see one who has ever been cured by such therapy. If these patients are watched long enough, their condition will be found to recur. I should like to refer to a paper published 20 years ago by Dr. Keschner and me (*J. Neurol. & Psychopath.* **21**:311, 1930). We reported several patients, all of whom had onset of their disease with a psychogenic picture and who were eventually seen in many clinics and by many observers. The final diagnosis was dystonia musculorum deformans.

DR. H. HOUSTON MERRITT: Some of your patients were temporarily improved by psychotherapy were they not?

DR. ABRAHAM M. RABINER, Brooklyn: Yes.

DR. RUBIN A. GERBER: Why is this paper called a psychiatric case study?

DR. HARRY STERLING, Brooklyn: The diagnosis of torticollis was made in the ward of the Neurological Institute, where the patient was for a seven-day period of observation and diagnostic study. I called it a psychiatric case study because I treated the patient psychiatrically only.

The patient took amphetamine (benzedrine®) and rabellon® (a compound of belladonna alkaloids) for several months, without benefit.

As to the changes in the position of the head, they have been only transient. The patient has, for the first time since the onset of the torticollis, had periods when the position of his head was normal. He has been able to work. I think there has been an improvement, but I can only speculate on what the future holds.

I have read Dr. Rabiner's article, and I learned a great deal from it, particularly in regard to this case. However, in the treatment, the patient himself has gathered confidence because of the changes in his symptoms.

I should like to quote from his history. He has always liked to sing in choirs and to make speeches, but always before he sang he would feel a contraction in his penis, and immediately his head would begin to shake, and also turn. For the past month he has been able to sing solos without this feeling in his penis and without his head movements. A number of other things make me feel optimistic.

Patterson (*Rev. argent. neurol. y psiquiat.* **9**:135-146, 1946; abstracted, *Digest Neurol. & Psychiat. Inst. of Living* **15**:559, 1947) reported a review of a study of 21 patients with spasmodic torticollis, all of whom received psychotherapy. Five patients recovered; five showed notable improvement; seven had slight improvement, and four did not respond at all. The improvement achieved in 13 patients was maintained.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Anatomy and Embryology

RESPONSES OF AMBLYSTOMA LARVAE WITH THE MIDBRAIN REPLACED BY A SUPERNUMERARY MEDULLA. S. R. DETWILER, J. Exper. Zool. **110**:321 (April) 1949.

Replacement of the embryonic midbrain (stages 21 and 22) by a supernumerary medulla causes young Amblystoma larvae to exhibit a progressive decline in their swimming capacity between stage 40 and stage 46+. However, these larvae have better locomotor ability than have larvae in which the midbrain is replaced by anterior segments of the spinal cord. The swimming scores of both the above types of experimental larvae parallel those of the control larvae up to stage 40. In both experimental conditions the tectospinal tracts are absent; yet, since the larvae with the midbrain replaced by medulla have less locomotor failure than those in which spinal cord replaces midbrain, the extraneous medulla must partly compensate for the loss of midbrain. Augmentation of tracts arising in the medulla (bulbospinal tracts) may influence the spinal locomotor system. It is clear that the bulbospinal tracts have a part in coordinating and helping to sustain the swimming reflexes, although they appear to be secondary to the tectospinal tracts. The midbrain is most indispensable, for without it the locomotor performance of young larvae is greatly reduced; on the other hand, larvae with two midbrains (the supernumerary one replacing the medulla) exceed the controls in swimming ability.

In all cases the larvae with a supernumerary medulla possessed supernumerary ears. While none of the ears was perfect, there was a remarkable degree of differentiation, considering their heterotopic position. The results obtained substantiate earlier conclusions that the differentiation of the ear vesicle is dependent on the medulla.

REID, New Brunswick, N. J.

Physiology and Biochemistry

ISOLATION OF POLIOMYELITIS VIRUS FROM THE HEART IN FATAL CASES. C. W. JUNGEBLUT and J. E. EDWARDS, Am. J. Clin. Path. **21**:601 (July) 1951.

Jungeblut and Edwards, in investigating the etiology of the myocarditis of poliomyelitis, attempted virus-passage studies on fragments of medulla, spinal cord, and heart in the five fatal cases and of the liver in one case. One milliliter of a 10% suspension of tissue was injected intracerebrally into pairs of young Cynomolgus monkeys. Poliomyelitis virus was isolated from the spinal cord and heart in two cases, from the cord only in the third case, from the heart only in the fourth case, and not at all in the fifth case. Two strains of virus from the cord were passed through monkeys several times. Only one strain from the human heart could be passed. A majority of the paralyzed monkeys showed myocardial lesions.

On the basis of this evidence, the authors submit the hypothesis that the myocarditis seen in poliomyelitis is due to the virus itself.

FOLEY, Boston.

RECOVERY OF VIRUS FROM REGIONAL LYMPH NODES OF FATAL HUMAN CASES OF POLIOMYELITIS. H. A. WENNER and E. F. RABE, Am. J. M. Sc. **222**:292 (Sept.) 1951.

The axillary, inguinal, and mesenteric lymph nodes and pancreatic tissues of nine patients who died of rapidly fatal poliomyelitis were tested by titration and serum neutralization tests for the presence of virus. The virus was found in the axillary lymph nodes of six patients, the inguinal nodes of four, and the mesenteric nodes of four. It was not found in pancreatic tissue.

BERLIN, Mount Vernon, N. Y.

EFFECTS OF STREPTOMYCIN UPON THE HUMAN FETUS. A. RUBIN, J. WINSTON, and M. L. RUTLEDGE, A. M. A. Am. J. Dis. Child. **82**:14 (July) 1951.

It has been suggested by experimental work on rats that the immature organism may be more susceptible to the neurotoxic effects of streptomycin than the adult. Since streptomycin crosses the placenta, the possibility of fetal damage from prolonged administration of the drug merits consideration.

Rubin and his colleagues treated three women with active tuberculosis with streptomycin during middle and late pregnancy. Prior to the birth of each infant, the mothers received streptomycin for periods ranging from 23 to 40 days and in doses totaling 23 to 40 gm.

Careful neurologic examinations (including tests of vestibular function with the Bárány technique) repeated upon the infants at frequent intervals up to 1½ years following delivery revealed no evidence of damage from the drug. Although two of the infants were born prematurely (cause unknown), their general development was normal up to the time of this report.

The authors suggest, from this limited experience, that the fetus is safe from the possible neurotoxic effects of streptomycin when the mother receives the drug.

ALPERS, Philadelphia.

A HORMONAL NEUROGENIC VASOPRESSOR MECHANISM. R. D. TAYLOR, I. H. PAGE, and A. C. CORCORAN, A. M. A. Arch. Int. Med. **88**:1 (July) 1951.

Cross circulation experiments and observations in dogs with spinal cords pithed below the sixth cervical segment and both vagus nerves cut in the neck confirm the liberation into the blood of a vasopressor substance on centripetal stimulation. This substance is shown by Taylor and his colleagues to be distinct from epinephrine, arterenol (nor-epinephrine), renin, angiotonin, and vasopressin U. S. P. Its activity is enhanced by large doses of tetraethylammonium chloride and inhibited and ultimately abolished by *l*-hydrazinophthalazine (C-5968). This drug also inhibits the pressor action of serotonin.

The authors believe that on appropriate stimulation the brain can act as an endocrine organ, releasing a pressor substance into the blood. They found that the therapeutic properties of a phthalazine derivative (C-5968) in human beings and in dogs with hypertension of varied origins are consistent with this hypothesis.

ALPERS, Philadelphia.

COEXISTENT GASTRODUODENAL AND CEREBRAL LESIONS IN INFANCY AND CHILDHOOD. H. G. SCHLUMBERGER, A. M. A. Arch. Path. **52**:43 (July) 1951.

Schlumberger reports that among 251 consecutive autopsies on infants and children there were 7 cases of acute duodenal ulcer, 2 of gastromalacia, and 1 of multiple acute gastric ulcer. All the conditions were associated with cerebral lesions in the following distribution; tuberculous meningoencephalitis, three cases; bulbar poliomyelitis, two cases; edema and anoxia, two cases, and intraventricular hemorrhage, sinus thrombosis, and microcephaly, one case each.

The causative relationship between cerebral lesions and acute gastroduodenal ulcer are multiple and complex. The integrating factors may be nervous or humoral, and perhaps oftenest both. The neural mechanism is probably that suggested by Cushing, viz., stimulation of a parasympathetic center in the diencephalon, which secondarily activates cranioautonomic nuclei, especially the dorsal nucleus of the vagus nerve. The resultant autonomic imbalance produces local ischemia or pronounced hyperemia with stasis and increased capillary permeability. Either of these vascular changes leads to anoxia and tissue damage, with decreased resistance to the action of the gastric juice. Besides vasomotor control, the motility of the gastrointestinal tract and the quantity and quality of the digestive juices are under the direct influence of the hypothalamus. Increase in gastric hydrochloric acid or pepsin and/or a decrease in the neutralizing bile or pancreatic juice may be important in the production of gastroduodenal ulcer.

WINKELMAN, Philadelphia.

EFFECTS OF SYMPATHECTOMY ON THE CEREBRAL CIRCULATION OF HYPERTENSIVE PATIENTS. H. A. SHENKIN, J. H. HAFKENSCHIEL, and S. S. KETY, Arch. Surg. **61**:319 (Aug.) 1950.

In nine patients suffering from arterial hypertension, the cerebral blood flow, cerebral oxygen consumption, and cerebral vascular resistance were studied before and after dorsal or dorsolumbar sympathectomy with splanchnicectomy. The cerebral blood flow and the cerebral oxygen consumption remained unchanged after operation, but the cerebral vascular resistance was decreased in eight of the nine patients (average decrease, 18%). There was also a postoperative fall in the oxygen content of the arterial and internal jugular venous blood. The type of operation, whether it was a dorsal sympathectomy and splanchnicectomy (Peet procedure) or the more extensive Smithwick dorsolumbar sympathectomy, had no significant effect on these results. The decrease in cerebral vascular resistance permits the cerebral blood flow to be maintained at a normal level despite the postoperative lowering of blood pressure. The authors assume that the postoperative lowering of vascular resistance may be due partially to reduced viscosity of the blood. It is worthy of mention that temporary sympathetic block with procaine produced no significant change in cerebral vascular resistance. The cerebral blood flow is presumably controlled by the carotid-sinus reflex. The diminished intracarotid pressure following sympathectomy changes the stimulation of the carotid-sinus mechanism, which, in turn, results in relaxation of cerebral vasoconstriction. The lowering of cerebral vascular resistance in hypertensive patients treated surgically may account for the beneficial effect of the operation on the cerebral symptoms and on the retinal changes.

LIST, Grand Rapids, Mich.

EXPERIMENTAL AND CLINICAL OBSERVATIONS ON RISING INTRACRANIAL PRESSURE. J. P. EVANS, and others, A. M. A. Arch. Surg. **63**:107 (July) 1951.

In the monkey and in the dog, arterial hypertension develops when the intracranial pressure approximates the blood pressure. In man, however, intracranial pressure may be raised by intrathecal injection of saline solution to or slightly above the level of the blood pressure, without producing an immediate effect on the pulse, blood pressure, or respirations. This experimental increase of intracranial pressure was higher than that usually observed with pathological conditions, such as brain tumors. The impairment of cerebral blood flow resulting from increase of intracranial pressure is compensated by immediate reflex dilatation of cerebral arteries, rather than by a primary rise of blood pressure. The "Cushing triad," viz., hypertension, bradycardia, and apnea, is therefore not a reliable criterion for the evaluation of increased intracranial pressure in man.

LIST, Grand Rapids, Mich.

CIRCULATORY DYNAMICS BEFORE AND AFTER EXERCISE IN SUBJECTS WITH AND WITHOUT STRUCTURAL HEART DISEASE DURING ANXIETY AND RELAXATION. I. P. STEVENSON, C. H. DUNCAN, and H. G. WOLF, J. Clin. Invest. **28**:1534 (Nov.) 1949.

Intolerance to exercise is a frequent complaint of patients with anxiety and of patients with conditions described under the heading of "neurocirculatory asthenia." It has also been found that healthy subjects without complaints or evidence of cardiovascular disease will under stressful conditions associated with disturbing emotional states, such as anxiety and resentment, show impaired exercise tolerance, as judged by excessive increases in heart rate, stroke volume, or both, during exercise. The present study was designed to investigate the relation of these observations by exploring the occurrence and range of impaired exercise tolerance in a group of healthy subjects without complaints and in a group of patients with and without structural heart disease who had complaints of effort intolerance.

A study was made of heart rate, blood pressure, and cardiac output before and after a standard exercise test.

The average cardiac outputs of subjects who were slightly disturbed emotionally were greater before and after exercise than those of subjects who were apparently relaxed. The difference was largely attributable to increases in stroke volume. The average cardiac outputs of subjects with strong overt anxiety were greater before and after exercise than those of the poorly relaxed subjects. This difference was largely attributable to greater increases in heart rate.

In general, there was a close correlation of such symptoms as dyspnea and palpitation with weakness on exertion and impaired exercise tolerance.

In 10 subjects with structural heart disease studied similarly, the same relation was found between emotional disturbances and the occurrence of symptoms and signs of effort intolerance. The symptoms themselves were those associated with cardiac failure.

The authors believe that the increased cardiac work and excessive tachycardia at rest and in response to exercise during anxiety may be relevant to the increased susceptibility of patients with tachycardia to the development of structural heart disease. ALPERS, Philadelphia.

FRONTAL LOBOTOMY: NEUROANATOMICAL OBSERVATIONS. P. I. YAKOVLEV, H. HAMLIN, and W. H. SWEET, J. Neuropath. & Exper. Neurol. **9**:250 (July) 1950.

Frontal lobotomy is now a widely used surgical procedure for the relief of certain mental disorders. The operation is performed, by and large, on patients whose mental illness has reduced them to a state of severe and long-standing social invalidism, carrying a reasonably certain prognosis of chronicity and of eventually irreversible deterioration.

In the case of death following lobotomy, occurring either as a result of operation or independently, diligent inquiry into the anatomic and pathologic changes in the brain should be made. The brains of six patients upon whom frontal lobotomy was performed were available for such a study. The specimens came from different sources, and operations were performed by different surgeons.

Neuropathologic study showed that in three specimens a more or less severe atrophic cerebral process had been present for some time before the operation. This would seem to indicate the need of roentgenographic study of the cranial contents prior to lobotomy, especially in the case of a patient who has been hospitalized for many years, such as the so-called deteriorated schizophrenic patient.

Cerebral lesions directly related to surgical procedures on the brain were of two orders: the mechanical dissolution of the continuity of the cerebral substance by the surgeon's instruments, and the necrosis of the tissues which were not directly damaged but became devitalized as a result of interference with their blood supply.

The extent and severity of parasurgical necrosis in this material seemed to be greater when the aspiration needle was used and less when the blunt leucotome was employed to sever the continuity of the cerebral substance in the frontal lobes.

The neuropathologic postoperative and intercurrent complications observed were (1) vascular; (2) local-infective, by extension from the scalp wound; (3) systemic-infective, by spread from visceral septic foci, and (4) cerebral metabolic changes.

Topographic study showed that as a rule the orbitomesial quadrant of the frontal lobe was severed bilaterally, involving the cingulate gyrus, while the dorsolateral, or convex, quadrants were largely spared. The symmetrical and consistently bilateral degeneration of the fibers in the dorsomesial or juxtacaudate part of the anterior limb of the internal capsule, in the subthalamic region, and in the rostromesial quadrant of the pons in cases of more than two-months postoperative survival was the most conspicuous anatomic finding.

The salient point of this anatomic study of lobotomy is that in all six specimens the cingulate gyrus was involved and the orbitomesial ectocortex (isocortex) of Areas 10 (FE), mesial 9 (FD), and 8 (FC) was undercut and isolated from the mesocortex (transitional cortex) of the cingulate gyrus (Area 24 [LA]) and the orbital limbus (posterior part of Area 11, corresponding to von Economo's fields FH, FHl, and FFa and the island of Reil [Areas 13 to 16 by Brodmann]). The rostral orbitomesial area of the frontal lobe of each side remained connected to the more primordial mesocortical parts of the brain only through the matricial synaptic groundwork (neuropil of Herrick and Coghill) of the convexial cortical plate and through its short and long arcuate associate systems. Not only the thalamofrontal radiations, but the pathway descending from the anterior half of the cerebral hemisphere to the brain stem and the spinal cord, was deprived of a large and important component of frontosubthalamic, frontopontine, and probably other corticifugal, fibers of the frontal lobe.

On the basis of this study, it seems to Yakovlev and his colleagues that the degeneration of the anterior-thalamic radiations and nuclei following frontal lobotomy has been stressed to the exclusion of the even more obvious degeneration of the far greater mass of efferent projections which connect the frontal lobes to all the levels of the neuraxis ("in series" and "in parallel").

These efferent projection systems are equally important and must be taken into consideration in the construction of a valid conceptual schema of the anatomicoclinical correlation of the frontal lobotomies (and other injuries to the brain) with the reorganization of the overt behavior which follows them.

ALPERS, Philadelphia.

CORTICAL PROJECTION OF VESTIBULAR AND FACIAL NERVES IN CAT. W. H. KEMPINSKY, J. Neurophysiol. **14**:203 (May) 1951.

The cortical receiving area of the vestibular portion of the eighth cranial nerve was outlined by single-shock stimulation of the "isolated" vestibular nerve in the cat. The center of the vestibular sensory area lies in the anterior descending limb of the suprasylvian gyrus. Anteriorly it overlaps the posterior margin of the tactile receiving areas of the arm and face, and posteriorly it appears to overlap the anterior margin of the auditory receiving area.

The ipsilateral and contralateral cortical projections are symmetrical in extent and location.

No cortical projection of possible afferent fibers of the facial nerve could be demonstrated, although Kempinsky states that one cannot exclude a projection from the nervus intermedius to this cortical region.

ALPERS, Philadelphia.

SITE AND EXTENSION OF BULBAR RESPIRATORY CENTRE. S. WOLDRING and M. N. J. DIRKEN, J. Neurophysiol. **14**:227 (May) 1951.

By means of localized recording of action potentials in respiratory rhythm and of localized stimulation of respiratory structures in the bulbar part of the medulla oblongata, two separate areas of the respiratory center were distinguished, a ventromedial inspiratory part and a dorsolateral expiratory part. The inspiratory area is situated mainly in the reticular substance at the level of the entrance of the vagi; the expiratory area seems to be connected with the spinal trigeminal root laterally and has medially a course parallel to the solitary tract.

ALPERS, Philadelphia.

THRESHOLDS OF CORTICAL REPRESENTATION. E. G. T. LIDDELL, and C. G. PHILLIPS, Brain **73**:9 (June) 1950.

Liddell and Phillips, using a "square-wave" stimulator and hexobarbitone (B. P.) anesthesia, have shown that the areas of representation of various movements in the motor cortex of the baboon can be made to vary in size according to the parameters of stimulation and the level of narcosis. Single pulses elicit movements confined to distal segments of the limbs and face. Boundaries of their cortical representation fluctuate with the strength of stimulation and the grade of narcosis, but actual movements vary little from preparation to preparation. The lowest threshold region is located in the middle third of the precentral gyrus; single pulses yield flick-like movements of the opposite thumb, index, and little finger. The threshold is higher for the toe complex and highest for the face complex as compared with that for the thumb complex. With stronger shocks and light narcosis the three areas overlap so widely that each shock causes flick-like movements simultaneously in all three peripheries from the greater part of the motor area. If repetitive stimuli of the same strength instead of single stimuli are applied, movements of all parts of the body, rather than movement of distal parts alone, occur. There is thus a change from a map of few effects and extensive areas, delineated by single shocks, to a map of many effects and narrow areas, delineated by repetitive stimulation. The latter grows into the traditional map of "motor points." The experiment supports the belief in wide fields of low excitability for the thumb-index, hallux, and face.

FRANKEL, Philadelphia.

CORTICAL RHYTHMS NOT SEEN IN THE ELECTROENCEPHALOGRAM. D. WILLIAMS and G. PARSONS-SMITH, Brain **73**:191 (June) 1950.

Williams and Parsons-Smith made recordings from surface electrodes and simultaneously from a series of point electrodes at different depths in the cerebral substance. Usually the electroencephalogram and the electrocorticogram revealed similar recordings, but in two instances this was not the case. One patient showed abnormal rhythms and random waves of high voltage, with frequencies ranging from 1 to 7 cps in the cortex; these abnormalities were not evident in

the electroencephalogram. In the second patient, recordings from the cortex showed rhythms with a frequency of 8 cps and a high voltage. These changes, too, were not present in simultaneously recorded electroencephalograms. On the basis of these two cases, the authors contend that records made from electrodes on a scalp may not represent the spontaneous rhythms arising in the cortex, since potential changes are occurring through the depth of the cortex from many points but reach its surface synchronously.

FRANKEL, Philadelphia.

SENSORY CHANGES IN PROCAINE NERVE BLOCK. D. C. SINCLAIR and J. R. HINSHAW, Brain **73**:224 (June) 1950.

Sinclair and Hinshaw discuss the manner in which the various modalities of sensation disappear and return when a nerve trunk is blocked with procaine. The ulnar nerve was blocked in the ulnar groove, and the lateral popliteal nerve, at the neck of the fibula. Touch, pain, and temperature sensibilities were studied. Generally the order of sensory loss followed a relatively stereotyped pattern, with pain the first sensation to disappear and touch the last. However, in a given experiment, any desired order of sensory loss could be achieved by selection of either the test site or the stimulus or both. No evidence was found to indicate that the paralysis of any modality involves first the more proximal portion within the territory of the nerve affected and later the more distal portion; it is suggested that differences in the initial sensitivity of the skin in different parts of this territory may be responsible for the mode of spread of anesthesia.

FRANKEL, Philadelphia.

THE CHEMISTRY OF CEREBRAL CYSTS. J. N. CUMINGS, Brain **73**:244 (June) 1950.

Cumings analyzed the contents of 52 cysts obtained from cerebral tumors; the tumors were diagnosed histologically. He studied the cholesterol, alkaline-phosphatase, total-protein and albumin, hemobilirubin, mucoprotein, amino-acid-nitrogen, desoxyribose-nucleic-acid, and ribose-nucleic-acid contents of the cyst fluids. The results suggest that degeneration of the tumor initiates the formation of cerebral cysts, followed by transudation of fluids from blood vessels. In cysts found in association with hemangioblastomas and neurofibromas, no evidence of necrosis was found, and the results suggest that the fluid was formed from the blood. There was no characteristic chemical pattern for any type of cyst, but there were some features which could be of assistance in the diagnosis of the tumor type. A pituitary cyst usually had a high cholesterol content; secondary carcinoma was the only tumor in which there was an elevated alkaline-phosphatase content; malignant tumors were characterized by increased amino-acid-nitrogen, protein, and desoxyribose-nucleic-acid contents.

FRANKEL, Philadelphia.

THE CLINICAL SIGNIFICANCE OF FASCICULATIONS IN VOLUNTARY MUSCLE. R. S. SCHWAB, D. STAFFORD-CLARK and J. S. PRICHARD, Brit. M. J. **2**:209 (July 28) 1951.

Schwab and associates compared the electromyographic and clinical observations on 15 patients with benign fasciculations and 1 patient with a distal type of muscular dystrophy with those in patients whose fasciculations formed an accompaniment to progressive muscular atrophy. The authors concluded that "benign fasciculations are comparatively common, particularly in relation to emotional stress, that they are distinguishable electromyographically from those associated with muscular degeneration, and that patients displaying them can also be differentiated clinically from patients with progressive muscular atrophy at a reasonably early stage." They draw attention to the liability of medically trained people to suffer considerable avoidable anxiety when such distinction is not clearly made.

ECHOLS, New Orleans.

A METHOD OF MEASURING REFLEX TIMES APPLIED IN SCIATICA AND OTHER CONDITIONS DUE TO NERVE-ROOT COMPRESSION. D. S. MALCOLM, J. Neurol., Neurosurg. & Psychiat. **14**:15 (Feb.) 1951.

It is well known that in sciatica and other clinical conditions resulting from compression of a nerve root by a prolapsed intervertebral disk, disturbances of the tendon reflexes may occur. In sciatica, diminution, or even absence, of the ankle jerk is a common finding. Sometimes, however,

this disturbance is slight and cannot readily be shown by the ordinary clinical tests. The present investigation was undertaken to assess the slighter degrees of impairment and to elucidate its mechanism.

The reflex time of the knee jerk and ankle jerk was measured by a special method. This study showed how constant the reflex time is in health and in disease, being unaffected in metabolic disturbances and with lesions of the pyramidal, extrapyramidal, and cerebellar tracts. A longer reflex time was found on the affected side in patients with lesions which produce unilateral nerve-root compression.

These delays in the reflex time result from the slowing of the passage of nerve impulses through the region of the compressed nerve root. The slowing of conduction is more pronounced and more constant when the actual nerve root affected is investigated than when the appropriate tendon jerk is examined. This is because more than one root enters into the reflex, and as the second and third roots may be normal, the delay may be less apparent.

ALPERS, Philadelphia.

REPETITIVE DISCHARGES IN HUMAN MOTOR NERVE FIBRES DURING THE POST-ISCHAEMIC STATE. E. KUGELBERG and W. COBB, J. Neurol., Neurosurg. & Psychiat. **14**:88 (May) 1951.

The repetitive discharges in muscle which occur after the release of a limb from ischemia have been variously considered as arising in proximal nerve or in distal structures, particularly the myoneural junctions.

When two pneumatic cuffs were inflated on the upper arm and, after a suitable interval, only the upper cuff was released, a repetitive discharge occurred in the first dorsal interosseus muscle on shock stimulation of the ulnar nerve. The distal stretch of the nerve and muscle was still ischemic, so that the repetitive tendency must have developed in that stretch of nerve which had been released from ischemia.

With the same arrangement of cuffs, repetitive discharges occurred in response to a slowly increasing electrical stimulus or to voluntary contraction of the muscle, and also spontaneously.

Owing to individual variations in the onset of ischemic nerve block and postischemic repetition, as well as to the fact that nerve block occurs more readily in proximal nerves, more consistent results were obtained when one cuff of the pair was on the forearm.

The authors discounted the possibility of spontaneous repetitive discharges being of reflex causation by blocking the ulnar nerve in the ischemic area with lidocaine hydrochloride. They discuss the bearing of their observations on the parallel postischemic sensory phenomena.

ALPERS, Philadelphia.

ELECTRICAL PAINS PROVOKED BY FLEXION OF THE NECK. T. ALAJOUANINE, R. THUREL, and C. PAPALOANOU, Rev. neurol. **81**:89, 1949.

The authors state that the sign of Lhermitte has value if the following criteria are carefully observed: production by flexion of the head of rapid, simultaneously appearing electrical pain over a large portion of the body, spreading from above downward along the spinal column, and oftenest to the lower extremities, with or without participation of the upper extremities. They do not agree with Lhermitte that the sign is an analogue of Tinel's sign in peripheral nerve injuries, and due to the sensitivity of demyelinated axis-cylinders, as in multiple sclerosis. They report 10 cases in which the sign was present. These represented various conditions involving the posterior columns, e. g., tumors, adhesions, and arachnoiditis. They observe that the sensation is produced at operations with local anesthesia by accidental percussion or other mechanical stimulation of the posterior columns.

The production of segmental or radicular paresthesias by flexion of the head is indicative of lesions along the course of the roots involved, even though this may be in the lower regions of the cord. The mechanism at play is traction on the entire cord; parasensations are elicited by immobility at the affected site, with traction elicited when the neck is flexed. If the response is the typical Lhermitte sign, mechanical interference with the posterior columns is indicated, and the lesion is likely to be in the cervical region.

LEGAULT, Washington, D. C.

IMPEDANCE OF THE HUMAN HEAD AS OBSERVED DURING ELECTRO-SHOCK TREATMENT. C. W. UMLAUF, R. C. GUNTER JR., and W. W. TUNNICLIFFE, Confinia neurol. **11**:129, 1951.

The authors have studied impedance across the human head over the range of voltage and current values commonly used in electroshock therapy. No correlation could be demonstrated between impedance and direct-current skin resistance, or between impedance and head size. Impedance had an inverse relation to current and voltage increase, and with the higher voltage and current values it had a tendency to level off at about 200 ohms. Within the usual voltage range of 60 to 160 volts impedance was in the range of 200 to 300 ohms. FOLEY, Boston.

STAB SENSATION AND THE STEREOTYPED REACTION TO STIMULATION OF THE PARIETAL PERITONEUM. A. AUERSPERG, O. AIDAR, and S. A. DE BARROS, Arq. neuro-psiquiat. **7**:393 (Dec.) 1949.

The authors tested the effect of thermal stimulation of the parietal peritoneum with the bulb of a peritoneoscope which was introduced after perforating the abdominal wall. The patient described the sensation accompanying this maneuver as a sharp pain or stabbing sensation. He localized the site of stimulation by pointing a finger to the part of the abdomen where he felt the stab. This could easily be checked because the light of the instrument could be seen through the abdominal wall in a darkened room. The pain caused by touching the peritoneal wall with the electric bulb was exactly that described by Capps and Coleman resulting from mechanical stimulation (Experimental Observation on Localization of Pain Sense Parietal and Diaphragmatic Peritoneum, *Arch. Int. Med.* **30**:778 [Dec.] 1922). It means, therefore, that the parietal peritoneum always responds in the same way regardless of the mode of stimulation. Stimulation of the walls of the viscera did not cause pain. One of the patients reported the stab sensation on the homologous contralateral side of the abdominal wall. All the patients localized the sensation accurately. N. SAVITSKY, New York.

EFFECT OF HIGH FREQUENCY SOUND WAVES UPON THE VESTIBULAR APPARATUS. E. VYSLONZIL, Wien. med. Wchnschr. **61**:468 (July 29) 1949.

On the basis of animal experiments, the author concludes that by varying the intensity of the sound waves it is possible to produce effects ranging from mild impairment to complete abolition of function of the vestibular apparatus. Very small doses sufficient to dampen the vestibular irritability do not affect the equilibrium and do not produce histologic changes except for mild hyperemia. In more intense experiments the maintenance of equilibrium may be rendered impossible without the animal being affected in any other way, so that follow-up studies over a period of months are possible. In these cases changes in the nerve tissue, as well as marked chronic hyperemia, are present. MASON, New York.

HISTAMINE AS SPECIFIC CONSTITUENT OF CERTAIN AUTONOMIC NERVE FIBERS. U. S. VON EULER, Acta physiol. Scandinav. **19**:85, 1949.

Von Euler studied the distribution of histamine in the central nervous system and in nerves, chiefly of cattle. Nerves were dissected out within an hour after death, finely cut, and extracted with 5 or 10% trichloroacetic acid. The trichloroacetic acid gave a 30 to 100% higher yield than did acid alcohol. Histamine was a constant ingredient in extracts of the central nervous system and of peripheral nerves, though the relative amounts varied greatly. The highest amounts, equivalent to some 60 to 100 γ of histamine dihydrochloride per gram, were found in nerves containing postganglionic sympathetic fibers, such as the splenic, the splanchnic, and the mesenterial nerves. The central nervous system and the spinal roots contained the lowest amounts. Nerves, including preganglionic autonomic fibers, like some cerebral nerves, contained intermediate amounts. The specific distribution of histamine indicates the presence of a special histaminergic system anatomically associated with the sympathetic system. The role of the histaminic nerves is tentatively correlated to secretory and smooth-muscle-regulating functions. J. A. M. A.

Neuropathology

DYSTROPHIA MYOTONICA AND MYOTONIA CONGENITA: HISTOPATHOLOGIC STUDIES WITH SPECIAL REFERENCE TO CHANGES IN THE MUSCLES. G. WOHLFART, J. Neuropath. & Exper. Neurol. **10**:109 (April) 1951.

Wohlfart reports studies made in 19 cases of dystrophia myotonica and 5 cases of myotonia congenita. Autopsy was performed in one case of dystrophia myotonica in which the spinal cord, sympathetic chain, peripheral nerves, and muscles were investigated histopathologically. Muscle biopsies were done in the other cases.

In the case of dystrophia myotonica with autopsy no histopathologic changes were observed in the spinal cord, the sympathetic chain, or the peripheral nerves. Fiber analysis by a special method revealed no pathologic change in the ventral or dorsal spinal roots.

Microscopic changes in the muscles were found to be, under certain conditions, pathognomonic of the disease in question. Wohlfart calls attention to the following points: 1. The only constant histopathologic change in dystrophia myotonica is an inward migration of nuclei from the periphery of the muscle fibers to the center, where they divide and form long chains. The migrating cells lose their immediate contact with the capillaries. Capillary loops and surrounding tissues are inclined to grow into the muscle fibers toward the nuclear rows. 2. In dystrophia myotonica the myofibrils are often destroyed without a corresponding decrease in the sarcoplasm content. 3. The striated fibrillar rings (striated annulets, the *Ringbinden* of Heidenhain, which were described by him as specific for myotonia) are rather common in dystrophia myotonica. However, they are also to be found in many muscles of advanced age and, especially, in the extrinsic muscles of the eye, as well as in muscular atrophy from disease and in progressive muscular dystrophy. 4. The histopathologic changes in myotonia congenita consist mainly of general hypertrophy of the muscle fibers and slight alterations which are reminiscent of the changes encountered in the early stages of dystrophia myotonica.

ALPERS, Philadelphia.

HALLERVORDEN-SPATZ DISEASE AND DYSTONIA. M. G. NETSKY, D. SPIRO, and H. M. ZIMMERMAN, J. Neuropath. & Exper. Neurol. **10**:125 (April) 1951.

Eight cases of Hallervorden-Spatz disease with autopsy are recorded in the literature. The authors add two pathologically verified cases to that number. In one, the clinical syndromes of dystonia musculorum deformans and Friedreich's ataxia were present. In the other, no clinical evidence of neurologic disorder was obtained, demonstrating that the pathologic picture may be present in a patient with no clinical signs or symptoms.

A review of the reported cases of Hallervorden-Spatz disease reveals that they are characterized pathologically by deposition in the globus pallidus and the pars reticularis of the substantia nigra of relatively large amounts of a pigment containing iron, fat, and some calcium. The pallidal cells are altered or destroyed. Usually, the striatum is involved, but to a less degree. Variable changes are seen also in the cerebellum and the cerebral cortex. Demyelination of the involved areas may or may not be present.

The clinical features common to most cases are a positive family history, presence of hereditary stigmas, onset between the ages of 6 to 14 years, presence of rigidity and/or involuntary movements, absence of sensory changes, progressive mental deterioration, and gradual decline over a period of about 12 years.

The possibility that an alteration of iron metabolism is the defect present in dystonia was investigated by study of four other cases of the syndrome, but they disclosed no abnormal iron pigment. The authors conclude that dystonia is a symptom complex which may be found in association with various pathologic changes.

Since Hallervorden-Spatz disease is a clinicopathologic entity, the authors do not classify the second case as an instance of this disease.

ALPERS, Philadelphia.

COMPARATIVE MORPHOLOGIC AND HISTOMETABOLIC STUDIES OF NERVE CELLS IN BRAIN BIOPSIES AND TOPECTOMIES. L. ROIZIN, J. Neuropath. & Exper. Neurol. **10**:177 (April) 1951.

Roizin attempts to correlate the morphologic and histochemical components of certain brain neurons. The material was obtained from 4 brain biopsies and 22 topectomies performed on

21 schizophrenic and 2 psychoneurotic patients and on 1 patient with involutional psychosis. All were subjected, prior to psychosurgery, to insulin- or electric-shock therapy or to both.

Roizin found that a morphologic variability (as illustrated by the Nissl method) of the medium and large pyramidal cells in the brain from selected biopsy and topectomy specimens is associated with decided variability in the activity of the indophenol oxidase (cytochrome-c oxidase), peroxidases, and acid phosphatases. Generally, the oxidase and peroxidase reactions follow very closely the microscopic features and the distribution of Nissl bodies. The acid phosphatases appear frequently more concentrated in the intracellular areas of more pronounced chromatolysis. Irregularity in reaction and distribution of acid phosphatases are common in various degenerative changes of the nerve cells. Decrease and rarefaction of the granular material of the reacting substrate are encountered in the pyknotic and ischemic types of neuronal changes. There is an apparent close similarity between peroxidase activity of the protoplasmic components of the studied neurons and some components of the fluid and corpusculated blood elements.

There are concomitant variations in the morphology and enzyme activity of the neurons and in the glial elements involved in the process of pseudoneuronophagia and neuronophagia.

Whether these variations in the correlated morphologic and histometabolic findings of the cortical cells investigated are due to changes in their functional activity, or to some, as yet, undetermined conditions is left open to further investigations.

ALPERS, Philadelphia.

EFFECT OF MORPHINE ON CATS WITH HYPOTHALAMIC LESIONS. W. R. MCCRUM and W. R. INGRAM, J. Neuropath. & Exper. Neurol. **10**:190 (April) 1951.

The purpose of this investigation was to determine, as far as possible, whether or not the hyperthermia and excitant action produced by morphine are dependent on the integrity of hypothalamic centers, as demonstrated by administering morphine to cats which were poikilothermic or cataleptic or both, with appropriate controls.

A group of normal cats were given injections of morphine sulfate, ranging from 5 to 35 mg. per kilogram of body weight, and in every case there were a marked rise in rectal temperature and an increased amount of body activity, which, if permitted, reached a convulsive level.

In order to locate possible sites of action of morphine in the central nervous system, electrolytic lesions were placed stereotactically in the caudal portion of the hypothalamus and the upper tegmentum in 10 cats. Four of the animals in which the lesions were presumably not in critical areas showed nearly normal postoperative behavior, and their reactions to morphine were those seen characteristically in normal animals. Six animals showed postoperative loss of temperature control and chronic somnolence, and in these animals the response to injection of morphine was greatly altered; hyperthermia and hyperactivity did not appear.

A cataleptoid state was present in some of the surgically treated animals of both groups and appeared independent of other behavior patterns. This condition did not seem to affect the animals reaction to morphine.

ALPERS, Philadelphia.

OBSERVATIONS ON CEREBRAL ARTERIOSCLEROSIS. G. EROS, J. Neuropath. & Exper. Neurol. **10**:259 (July) 1951.

The main object of this paper was to record observations on the histogenesis of cerebral arteriosclerosis and the sequence of the morphologic changes in the affected cerebral vessels. The material used consisted of 52 brains which were fully examined and of 36 brains which were only partially inspected as a check on the several types of vascular and parenchymatous changes observed in the fully examined brains. In all cases the diagnosis of cerebral arteriosclerosis was made either clinically or on gross postmortem examination.

From this detailed study, Eros found that the primary changes in the arteries in cerebral arteriosclerosis are mainly alterations in the elastic tissue. The elastic-tissue changes permit the recognition of two main types of cerebral arteriosclerosis: (1) the hyperplastic degenerative and (2) the hypoplastic degenerative type. The first is characterized by primary proliferation of the elastica; the second, by the primary degeneration of the constitutionally hypoplastic elastica.

The type of vascular changes, the type of parenchymatous changes, and the clinical manifestations seem to show a definite relation. Focal neurologic symptoms are more prevalent in

the hyperplastic than in the hypoplastic type. In the hypoplastic type the mental symptoms are usually much severer than in the hyperplastic type. Delusions and hallucinations are often encountered in the hypoplastic type and are rare in the hyperplastic type. In the hyperplastic type the more severe mental symptoms develop late in the course; at the beginning irritability, nervousness, and emotional instability are in the foreground. In the hypoplastic type severe mental symptoms, often resembling schizophrenia, may develop rather early.

The development of the two types of vascular changes seems to depend upon the constitutional make-up of the affected vessels, and the vascular changes are likely to be precipitated by long-standing functional disturbances of the cerebral circulation, especially those occurring in hypertension.

ALPERS, Philadelphia.

HISTOPHYSIOLOGICAL EFFECTS OF ARSENIC AND ITS DERIVATIVES ON THE CENTRAL NERVOUS SYSTEM AND PARTICULARLY ON THE THIRD ELEMENT OF THE CENTRAL NERVOUS SYSTEM. S. GRZYCKI and B. KOBUSOWNA, J. Neuropath. & Exper. Neurol. **10**:325 (July) 1951.

The authors undertook the present study, on the basis of histochemical methods used for the detection of arsenic in the brain, to determine (1) which cells of the central nervous system possess phagocytic powers for arsenic and its compounds, and (2) what is the character of the cell changes, if any, in the cerebrum, the cerebellum, and the spinal cord as the result of administration of arsenic and its chemical compounds. Albino rabbits were used in the experiments.

It was found that arsenic and its compounds, regardless of the manner of its administration, is taken up and stored by the mesenchymal cells. It was found in the Kupffer cells in the endothelium of the sinuses and capillaries of the spleen, in the wandering and fixed histiocytes in the skin, and in the capillary endothelium of the lungs, heart, and kidneys. In the central nervous system, the phagocytic capacity for taking up arsenic and its compounds was first manifested by the capillary endothelium and then by the microglia cells of the gray and white matter of the cerebrum and cerebellum. The number of phagocytosed arsenical granules increased with the duration of administration of the drug; its presence affects the cytoplasm and the nucleus of the cells.

Regardless of the type of arsenical compound used, perivascular aggregations of the cellular elements make their appearance. Their number, however, depends on the quantity of the arsenic administered and on the changes produced by arsenic in the vascular endothelium. Around the blood vessels and the large nerve cells of the cerebral and cerebellar cortex and the gray matter of the spinal cord there are small fusiform cells capable of storing arsenic. The authors believe these are histiocytes. These cells, often spoken of as Hortega cells, are considered by him to be of mesenchymal origin. In addition to performing other functions, they play an active part in supplying substances, as well as in conveying the metabolic products from blood vessels to the nerve cells, and vice versa. They thus form a link between the blood vessels and the nerve tissue.

The results of this investigation seem to leave no doubt that the third element of the central nervous system is composed of the active mesenchymal cells, the microglia, existing mostly in the gray matter of the brain and cerebellum, and of the capillary endothelium of the cortex and the white matter of the brain, the cerebellum, and the spinal cord.

The presence of arsenic in the protoplasm of the microglia cells leads to damage of their nuclear structure, fatty degeneration of the cytoplasm, and, finally, complete destruction of the cell body.

No arsenical granules could be demonstrated by histochemical methods in the protoplasm of nerve cells.

Arsenic and its compounds stored up by the system of the active mesenchymal cells remained in the animal organism for some time. For as long as 30 days after its administration it was possible to detect numerous granules of arsenic in the capillary endothelium. In the Hortega cells, however, arsenic was no longer present. Thus, the removal of arsenic from the animal organism probably takes place via the blood vessels, and it is eliminated by the kidneys.

ALPERS, Philadelphia.

Psychiatry and Psychopathology

PSYCHOEDUCATIONAL STUDY OF CHILDREN BORN DEAF FOLLOWING MATERNAL RUBELLA IN PREGNANCY. E. S. LEVINE, A. M. A. Am. J. Dis. Child. **81**:627 (May) 1951.

The relation of rubella infection during early pregnancy to various congenital defects in the infant—notably acoustic defects—has been confirmed by reports from various workers throughout the world. It was considered timely to investigate the psychoeducational patterns of children born deaf after rubella in the mother during pregnancy. This paper, accordingly, is based on a study of the behavior, intelligence, school achievement, acoustic patterns, and general health of 16 such children in their first two years of school life. Their ages at the time of school admission ranged from 3 years to 4 years 10 months.

In all cases rubella had been contracted by the mother within the first three months of pregnancy. Other physical defects present among the children included ocular defects, systolic murmur, cervical adenitis, umbilical hernia, pigeon breast, enlarged spleen, aphagia, digestive disorder, and cryptorchism.

In regard to behavior, 13 of the 16 children behaved much the same as the other inmates at the school for the deaf, except for their greater tendency to hyperactivity, tenseness, and low stimulus threshold. In the other three children, however, the behavior was strongly suggestive of cerebral damage or disease, combining infantile characteristics, defective mentality, inappropriate responsiveness, and queer mannerisms.

Intelligence testing of the 13 children to whom such tests could be successfully administered disclosed a range from borderline through superior, and their school progress was in accordance with their respective mental capacities. The three seriously affected children could not be tested successfully. At the end of a special two-year class project it was decided that they were uneducable, and institutional care was recommended.

From the evidence of this study, it appears that deaf children with a maternal history of rubella during pregnancy fall into two main classes, educationally considered: (1) those who are educable and in whom the major developmental handicap is deafness, and (2) those who are uneducable and in whom the developmental handicaps are deafness, mental defect, and behavioral peculiarities suggestive of cerebral damage. The evidence further indicates that developmental peculiarities make themselves apparent as far back as early infancy. In such case it is wise to prepare the parents for the possibility of institutionalization of the child. For the same reason, the association between congenital defects and maternal rubella during pregnancy should be given wide publicity in order that parents and children both may be protected against this relatively mild illness, which may, nevertheless, have such serious consequences.

ALPERS, Philadelphia.

CEREBRAL PALSY IN RELATION TO DEVELOPMENT. B. CROTHERS, A. M. A. Am. J. Dis. Child. **82**:1 (July) 1951.

Crothers discusses the mother-child unit during pregnancy, and traces it through the normal mother-child relationship, to the rebellion of adolescence, and eventually to adult maturity. He points out the great confusion existing in this relationship in the cases of cerebral paralysis.

From the point of view of the child, protection is more absolute than it should be; social freedom is delayed; irregularities in mental ability make school progress difficult, and, finally, the normal explorations and rebellions of adolescence are more complicated.

From the point of view of the various adults who are desperately trying to help the child, the situation is frustrating. Intense desire to make up for the disabilities leads parents to prolong the period of absolute protection and, at the same time, to interfere constantly by putting on pressure. The result is that the element of adult intervention is exaggerated, while the chance to grow up is almost ignored.

In discussing how children with cerebral paralysis should be cared for, the author points out that, unlike the blind or the deaf, we have no present evidence about the adult careers of any important number of such patients who have been carefully supervised as children. He believes that what we need above all is a study that carries the investigation of development through the years of maturity. The problems of cerebral paralysis will become clearer as we learn enough to organize the infinitely varied cases into groups which can be regarded as approximately uniform.

The present situation is disturbing, with enormously complicated teams of people being used as teachers and protectors, without any clear notion of what will happen when artificial and expensive support is withdrawn. The problem has been set in terms of protection in childhood, when it should be approached in terms of modification of independence in adult life.

ALPERS, Philadelphia.

PSYCHOLOGIC STUDIES AS AIDS IN DIFFERENTIAL DIAGNOSIS OF BRUCELLOSIS AND PSYCHONEUROSIS. HAROLD J. HARRIS, Dis. Nerv. System **9**:364 (Dec.) 1948.

Recognizing the difficulty in distinguishing between psychoneurosis and chronic brucellosis and in assigning to each the proper responsibility for incapacitation when the two coexist, Harris has studied the problem from the psychological standpoint, both in naval personnel and in private practice. The investigational methods employed have included interviews, amobarbital (amytal®) sodium sessions, use of the Cornell Selectee Index, Rorschach and other projective tests, and trial of psychotherapy. It is believed that a stubborn illness like brucellosis may allow expression of emotional imbalance in persons previously well adjusted, perhaps because of the frustrating nature of its long, drawn-out course. The batteries of tests were variously interpreted by the psychologists participating in the survey: Two found no personality pattern characteristic of the disease, while another noted uniform ego weakness, exaggerated ambition, tendency to anxiety hysteria, and avoidance of sexuality. The cases cited by the author illustrate the necessity of assessing and treating both the organic and the psychiatric factors in the patient afflicted with brucellosis.

BEATON, Tucson, Ariz.

PRELIMINARY REPORT OF SIXTY-TWO PREFRONTAL LOBOTOMIES ON PSYCHOTIC MALE VETERANS AT THE VETERANS HOSPITAL, NORTHPORT, LONG ISLAND, N. Y. L. DRUBIN, J. Nerv. & Ment. Dis. **112**:301 (Oct.) 1950.

Drubin reports on 3½ years of follow-up observation on 62 lobotomized patients, all but 2 of whom were schizophrenic. All patients had psychotherapy and other rehabilitative measures after the lobotomy. None of the patients was considered cured, and none was worse. Only 4% of the patients showed no change. The condition of 37% was greatly improved; that of 29% was moderately improved, and that of 27% was only slightly improved. Agitation was considered the chief criterion for selection for lobotomy, and only six patients showed agitation after operation. As for the postoperative behavior, most patients showed constricted interests and psychomotor and intellectual retardation. Many patients were still experiencing hallucinations and delusions, but were able to cover these up and were in better contact with reality. The younger patients showed a generally better response to the procedure than did the older patients. In 12 of the patients seizures developed. Postlobotomy electroencephalographic tracings were of little value in predicting which patients would have seizures.

BERLIN, Chicago.

Meninges and Blood Vessels

OCULAR COMPLICATIONS ENCOUNTERED IN INTRACRANIAL ARTERIOGRAPHY. H. F. FALLS, R. C. BASSETT, and A. E. LAMBERTS, A. M. A. Arch. Ophth. **45**:623 (June) 1951.

The authors had observed that intracranial angiography exhibited facial and conjunctival petechia postoperatively on the homolateral side. This observation instigated the present study.

Eighty consecutive cases of intracranial angiography were reviewed for evidence of ocular complications. Petechial hemorrhages of the eyelids, of the palpebral and bulbar conjunctiva, and of the retina were demonstrated. Pupillary dilatation, optic neuritis, angiospasm of the retinal vessels, and blindness were also encountered.

The cause of these complications is not known but Falls, Bassett, and Lamberts believe that they undoubtedly result from vascular change secondary to allergic, toxic, or physical phenomena.

ALPERS, Philadelphia.

OCCLUSION OF CENTRAL RETINAL VEIN IN MIGRAINE. M. W. FRIEDMAN, A. M. A. Arch. Ophth. **45**:678 (June) 1951.

Friedman tabulates the reported cases of permanent vascular damage to the eye as a complication of migraine and reports a case of occlusion of the central retinal vein associated with migraine.

In discussing the possible underlying pathologic processes in this condition, he points out that an attack of migraine may be divided into two phases. The first, or vasoconstriction, is the preheadache period. In this phase are found the visual phenomena generally associated with migraine. Scotomas are thought to result from spasms of the posterior cerebral artery, with resultant ischemia of portions of the occipital cortex. When spasm of the retinal arteries is severe, occlusion of the affected vessels may occur, leading to a permanent defect in the field of vision. The occasional development of retinal-artery occlusion offers direct and visible evidence of vasospasm in the early stages of a migraine attack, for it is probable that such occlusion leads to thrombosis and this thrombosis is secondary to spasm of the affected vessel. This vascular spasm is regarded as the cause of the transient focal symptoms so frequently associated with migraine, viz., scotomas, paresthesias, paresis of the extremities, and aphasia.

The second, or vasodilatory, phase accounts for the headache, nausea, and vomiting on the same basis as that of histamine toxicity, i. e., a direct function of dilatation of the cerebral vessels. The optic disks have been examined repeatedly at the time of both scotoma and headache, without, as a rule, any visible change; but veins have been engorged during the headaches and arteries constricted during the time of the scotoma, their caliber increasing with the return of vision.

To explain why a particular attack of migraine should precipitate irreversible vascular changes, or why these changes occur at all, it is postulated that the vascular changes undergone in the biphased migraine attack are in themselves sufficient to cause intimal damage and a rather localized atherosclerotic process. In the presence of cerebral atherosclerosis, however slight, crises of hemicrania are much more likely to be the cause of vascular accidents, such as hemorrhage and thrombosis, than would be the case with normal vessels.

Clinical and experimental observation suggests that the symptoms of migraine result from alteration of the caliber of the blood vessels in the head and that both intracranial and extracranial vessels take part in this process.

ALPERS, Philadelphia.

OPTO-CHIASMATIC ARACHNOIDITIS: SURGICAL TREATMENT AND RESULTS. G. H. DICKMANN, F. K. CRAMER, and A. D. KAPLAN, J. Neurosurg. **8**:355 (July) 1951.

Optochiasmatic arachnoiditis is fundamentally a neurovascular disturbance, which affects capillary permeability and produces exudative and cicatricial reactions. The leptomeningeal formations involving the optic nerves do not in themselves constitute the lesion but indicate the existence of focal neurovascular disturbances.

Endocrine disorders, allergic disturbances, infections of the paranasal cavities, neurovirus processes, syphilis, tuberculosis, and cranioencephalic trauma may all be precipitating factors, but in the authors' opinion neurovascular disturbance is the perfect explanation for the anatomic lesions and symptomatology of optochiasmatic arachnoiditis.

Dickmann and his co-workers state that treatment of this condition should be immediate and should aim at the correction of the predisposing condition and the modification of the factors in the onset of the neurovascular process, which is the actual cause of the formation of exudative, adhesive, and membranous leptomeningeal lesions. Operation is of benefit, once the optochiasmatic formations have set in, because of the mechanical liberation of the optic nerves and chiasm. The authors report a study of 47 patients operated on for optochiasmatic arachnoiditis.

In 63% of the cases postoperative results were considered unsuccessful. In the remaining 37% the operation brought about a variable degree of improvement or an arrest of the process.

It is pointed out that infiltration of the cervicothoracic sympathetic nerve, if carried out at an early date, can be of benefit in modifying the neurovascular condition.

ALPERS, Philadelphia.

DIAGNOSIS OF TRAUMATIC INTRACRANIAL HEMORRHAGE BY ANGIOGRAPHY. J. E. WEBSTER, R. DAWSON, and E. S. GURDJIAN, J. Neurosurg. **8**:368 (July) 1951.

Angiography was employed in this study in cases of major cranial injuries in which the patients did not improve under conservative management or presented evidence of a "dynamic syndrome" of increasing stupor, new focal signs, and cardiac, thermal, or respiratory evidence of progressive cerebral dysfunction. Thirty arteriographic studies were made.

Typical vascular patterns were found to distinguish the subdural, epidural, and intracerebral hematomas. Webster and his colleagues found angiography to be reliable. They believe the procedure is superior to the more complicated, and possibly inaccurate, exploratory trephination.

Unfortunately, there is a disadvantage in moving the patient for the roentgen studies. There is an additional risk when thiopental anesthesia is necessary for the uncooperative patient. The time consumed in obtaining the arteriogram is another consideration. However, arteriography appears to be useful, and more experience will give it its proper place among the diagnostic procedures for the better management of the seriously ill patient after head trauma.

ALPERS, Philadelphia.

DIODRAST STUDIES OF THE VERTEBRAL AND CRANIAL VENOUS SYSTEMS, TO SHOW THEIR PROBABLE ROLE IN CEREBRAL METASTASES. R. ANDERSON, J. Neurosurg. **8**:411 (July) 1951.

In a series of 1,076 verified cases of intracranial tumors reviewed by Anderson the incidence of metastatic tumors was found to be 8.4%. Cerebral metastatic lesions are blood-borne, since no lymphatics are present in the brain. The commonly accepted route of the vascular spread of tumor cells to the brain is along the arterial tree. However, other hematogenic modes of spread were postulated by Batson in 1940. By the use of various radiopaque substances injected into the venous systems of human cadavers, he demonstrated roentgenologically the ease with which the media could pass along the vertebral venous system; its close association with the veins of the body wall, and pelvic and shoulder girdles, and, finally, its continuity with the venous sinuses within the cranium.

In the present study, Anderson, employing iodopyracet and newer injection techniques (1) repeated the cadaver experiments (using 12 cadavers) and (2) showed that similar studies could safely be performed on living subjects to determine whether venous patterns obtained in cadaver studies would be found in the presence of normal circulating mechanisms. Twenty-two injections in living human subjects were performed.

By the above procedure, the elementary, segmental character of the vertebral venous system and its continuity with the cerebral venous sinuses were demonstrated roentgenologically. The close relationship of this venous system to the veins of other axial structures, such as the prostate, kidneys and adrenals, lungs, breast, and thyroid, were shown. The shunting of blood from the systemic circulation into the vertebral venous system was demonstrated roentgenologically in the living subjects.

Anderson considers that these studies have furnished further supportive evidence of possible routes for spread of metastases via the vertebral venous system from distant primary foci to the cerebrum.

ALPERS, Philadelphia.

CHRONIC OR SUBACUTE SUBDURAL HEMATOMA DUE TO INDIRECT HEAD TRAUMA. J. M. MEREDITH, J. Neurosurg. **8**:444 (July) 1951.

Practically all cases of chronic subdural hematoma are due to some type of direct head injury. In a survey of the world's medical literature for the past 10 years, the present reviewer encountered only a single instance of a chronic subdural hematoma due to indirect trauma, and the mode of the indirect injury was not available to him. Loyal Davis mentions a fall on the buttocks as the only known trauma in certain cases of chronic subdural hematoma but does not detail specific cases.

In the two cases described in this paper, one of subacute and one of chronic subdural hematoma, the etiologic factor was a fall on the buttocks. Neither patient was alcoholic or psychotic, and both were highly intelligent, so that an accurate history with respect to trauma of any kind was available for each. Each patient made a satisfactory recovery after evacuation of the subdural hematoma overlying the left cerebral hemisphere.

ALPERS, Philadelphia.

NEUROMUSCULAR DISORDERS AMENABLE TO WHEAT GERM OIL THERAPY. R. RABINOVITCH, W. C. GIBSON, and D. MCEACHERN, J. Neurol., Neurosurg. & Psychiat. **14**:95 (May) 1951.

One hundred and fifty-one patients with neuromuscular disorders were investigated and followed for periods varying from many months to 12 years. One hundred and seven of the patients were treated either with wheat germ oil or wheat germ oil concentrates, and sometimes with the addition of tocopherols. Thirteen showed definite improvement.

Improvement was noted in two cases of atypical muscular dystrophy. In 5 of 25 patients with progressive muscular dystrophy, symptoms were arrested, and moderate to pronounced improvement occurred. Three of five patients with menopausal muscular dystrophy showed remarkable improvement. All three patients with dermatomyositis responded favorably to wheat-germ-oil therapy.

Rabinovitch and his colleagues conclude that certain neuromuscular disorders respond to wheat-germ-oil therapy. These conditions are ones which are also apt to show improvement with the administration of adrenal corticoids.

ALPERS, Philadelphia.

CLINICAL FEATURES AND RESPONSE TO CORTISONE OF MENOPAUSAL MUSCULAR DYSTROPHY. G. M. SHY and D. MCEACHERN, J. Neurol., Neurosurg. & Psychiat. **14**:101 (May) 1951.

Shy and McEachern describe a form of myopathy which occurs predominantly in women during the climacteric period or after and appears to have characteristic features. Its recognition is of especial importance, since improvement may occur on treatment with wheat germ oil or cortisone.

Eleven women and one man were studied. Six of the women were treated with wheat germ oil, and four showed notable improvement. Five patients, four women (two of them from the wheat-germ-oil series) and one man, were treated with cortisone, with dramatic improvement in all. A maintenance dose of cortisone acetate is necessary.

The typical picture of this condition is that of progressive weakness (sometimes rapid, sometimes slow) of the hip and shoulder-girdle muscles. Examination of the individual muscles reveals their profound weakness, and palpation shows a "soft" consistency of the affected muscles. Visible wasting is unusual, perhaps because the patient is often well nourished, but occasionally the quadriceps femoris groups are seen to be atrophied. On the whole, the lower extremities are more severely affected than the upper, but this may be a reflection of the greater weight bearing of these structures. There is no complaint of facial weakness, difficulty in swallowing, or double vision, and power in the hands and feet remains normal.

Deep reflexes may be depressed in the muscles involved in proportion to the severity of the involvement. Most of the muscles contributing to the visual reflexes are relatively unaffected, however, and the usual reflexes are therefore often lively. No signs of central-nervous-system involvement have been elicited.

The authors emphasize the necessity of biopsy for diagnosis. Biopsy was always performed on the muscle most available and most affected clinically. The pathologic picture is that of a dystrophy.

At biopsy the muscle usually appears pale. On microscopic examination, the main abnormality observed is patchy degeneration or necrosis of individual fibers, usually accompanied with phagocytosis of these portions. There is usually proliferation of the sarcolemmal nuclei, and in some instances the only abnormality may be a central migration of the swollen sarcolemmal nuclei into the fiber. Aside from central migration of the nuclei, loss in cross striation is the earliest sign of muscle involvement. In advanced cases connective-tissue elements and fat are predominant.

ALPERS, Philadelphia.

Diseases of the Brain

HEMIPLEGIA FOLLOWING TONSILLECTOMY. J. F. B. ZWEIGHAFT, Anesthesiology **10**:729 (Nov.) 1949.

Zweighaft reports the case of a boy aged 5 years who was hospitalized for tonsillectomy and adenoidectomy. On the day after operation flaccid hemiplegia and peripheral facial paralysis were observed on the left side. A provisional diagnosis of polioencephalitis was made,

and later several other diagnoses were suggested. After four weeks in the hospital, the child was discharged with slight residual weakness in the left arm and left leg. Continued improvement was evident two months after the operation. The author suggests that a localized vascular accident was probably responsible for the hemiplegia in this patient. He discusses the role of the carotid sinus and suggests the possibility of producing cerebral damage by elevation or lowering of the blood pressure. Undue pressure on a sponge in the tonsillar fossa might act in either way. The author advocates the use of oxygen, rather than of air in bringing ether to the patient. The literature suggests that anesthesia is responsible for a small percentage of the neurologic complications of tonsillectomy. Induction of anesthesia for tonsillectomy should not be relegated to second-rate anesthetists; tonsillectomy may be a minor operation, but it certainly requires major anesthesia.

J. A. M. A.

Rheumatoid Arthritis with Death from Medullary Compression. F. W. Davis and H. E. Markley, Ann. Int. Med. **35**:451 (Aug.) 1951.

Rheumatoid arthritis, or Marie-Strümpell spondylitis, commonly involves the spine, and the upper cervical vertebrae are occasionally affected. Compression of the spinal cord by the extreme flexion observed in these processes has been recorded. Dislocation of the atlantoaxial joint has been observed in cases of active rheumatoid arthritis, with manifestations of medullary compression.

Davis and Markley observed a woman of 58 whose death was thought to have resulted from compression of the medulla oblongata by the odontoid process. In this patient the rheumatoid arthritic process, which had been active for many years, gradually produced bony destruction of the axis, atlas, and occiput, similar to that which occurred in the other weight-bearing joints. As necrosis and fragmentation advanced, compression and resulting deformity ensued. Herniation of the odontoid process was eventually of sufficient magnitude to encroach on the vital centers of the medulla, especially the respiratory center, and death resulted.

Microscopic sections of the region of the herniated odontoid process showed evidence of bone destruction and fragmentation, as well as fibrosis and new bone formation. Several areas of fresh collagen necrosis, typical of active rheumatoid disease, were seen both here and in sections of other joints.

The ganglion cells of the medulla showed pyknosis, eccentric nuclei, and vacuolation of cytoplasm. No demyelination was evident, and sections of other areas of the brain and cord were normal.

Alpers, Philadelphia.

Bacillus Proteus Abscess of Cerebellar Lobe of Otogenic Origin. W. R. Chambers and W. Clark, A. M. A. Arch. Otolaryng. **54**:179 (Aug.) 1951.

Chambers and Clark report the case of a youth aged 16 with cerebellar abscess and subdural abscess in the posterior fossa, of otogenic character and due to a Proteus-vulgaris infection. Cerebellar abscess from this source is rare, as is any brain abscess due to this infectious agent. In either of these circumstances prognosis has been poor in the past.

The patient was subjected to three operations and was discharged after 78 days in the hospital, having received 53.5 gm. of streptomycin, as well as 17,350,000 units of penicillin, 2,000 mg. of aureomycin, 55,750 mg. of chloramphenicol, 3.5 gm. of sulfadiazine, and 4 gm. of eskadiazine* (a 10% [W/V] aqueous solution of microcrystalline sulfadiazine). Two months after discharge he was able to ride a bicycle without difficulty, and all his residual neurological signs had improved.

Alpers, Philadelphia.

Effect of ACTH in Cerebromacular Degeneration. L. Gitman, S. Brusilow, and I. J. Greenblatt, J. Clin. Endocrinol. **11**:866 (Aug.) 1951.

Gitman, Brusilow, and Greenblatt report on the use of corticotropin in the treatment of an 18-month-old girl with Tay-Sachs disease (infantile amaurotic familial idiocy). A total of 1,000 mg. of corticotropin was administered over a period of 24 days. The adrenal cortex reacted normally, as demonstrated by hyperglycemia, eosinopenia, leukocytosis, and elevated urinary excretion of estrogens, 17-ketosteroids, and formaldehydogenic corticoids. The initially elevated

lipid phosphorus was reduced 60% during treatment, with a return to the previous high level on cessation of therapy. The serum cholesterol, originally following at a normal level, was also depressed while the child was under treatment. Reexamination four months after discontinuation of therapy revealed progressive deterioration, with the development of spasticity and hydrocephalus. In view of the normally reactive adrenal cortex, disturbance of function of the adrenal cortex may be excluded as an etiologic factor in cerebromacular degeneration.

FRANKEL, Philadelphia.

ICTAL AND NON-ICTAL PSYCHIATRIC DISORDERS IN TEMPORAL LOBE EPILEPSY. F. A. GIBBS, J. Nerv. & Ment. Dis. **113**:522 (June) 1951.

Psychomotor seizures are characterized by confusional episodes during which the patient executes coordinated, and apparently purposeful, activity. There may be associated personality disturbances and psychoses, but the nature of these is variable. The psychiatric symptoms may overshadow the epileptic manifestations. Of 275 cases of localized spike foci, the abnormality was localized in the anterior temporal lobe in 59%. Electrocorticograms showed the maximal seizure activity to be in the second temporal convolution. A higher incidence of psychiatric disorders occurred when there was a spike focus in the anterior temporal region than when it was in any other region.

BERLIN, Mount Vernon, N. Y.

PRIMARY PONTILE HEMORRHAGE WITH PARTICULAR REFERENCE TO RESPIRATORY FAILURE. A. T. STEEGMAN, J. Nerv. & Ment. Dis. **114**:35 (July) 1951.

In 17 cases in which hemorrhage into the pons was the primary lesion, the onset was characterized by the rapid development of coma and death, usually in less than 18 hours. In two cases there was toxemia of pregnancy, and in the rest hypertensive cardiovascular disease. In over 75% the cerebrospinal fluid was bloody. Bulbar paralysis was the commonest sign, but changes in the pupils, deep reflexes, muscular tone, and temperature were also present. Altered respiration, varying from suppression of respiratory rate and rhythm to respiratory failure, was observed in almost all cases.

BERLIN, Mount Vernon, N. Y.

HEMANGIOBLASTOMA OF CEREBELLUM WITH POLYCYTHEMIA. R. D. WOOLSEY, J. Neurosurg. **8**:447 (July) 1951.

Neurologic signs and symptoms are frequently associated with primary polycythemia, as a result of the vascular complications characteristic of this disease. Conversely, instances of intracranial neoplasms with associated secondary polycythemia have been reported. Woolsey presents the third reported case of hemangioblastoma of the cerebellum with associated polycythemia.

A man aged 24 had a cerebellar cyst removed. All blood studies at this time gave normal results. He remained well for approximately four years, at which time symptoms suggesting an intracranial lesion reappeared. The cerebellar craniotomy wound was reopened, and a mass, which proved to be a hemangioblastoma, was removed. The polycythemia did not develop until this large hemangioma was demonstrable.

Immediately after operation the red blood cell count and hemoglobin began to drop to normal levels and had remained so until the time of this report, two years after operation.

ALPERS, Philadelphia.

NEUROLOGIC ASPECTS OF FATIGUE. R. S. SCHWAB, and J. S. PRICHARD, Neurology **1**:133 (March-April) 1951.

Essentially four sites for the development of fatigue are seen in neurologic practice. The first is in the muscle itself. The second site of the disturbance, the myoneural junction, produces earlier fatigue in voluntary contraction. The third site of the involvement of fatigue is in the peripheral nerve or in the spinal cord. In the fourth group the fatigue is produced by the presence of excessive numbers of sensory impulses entering the nervous system beyond and above the normal ones from the muscle. This might occur in a patient with a painful joint around which the muscle is operating. A similar process takes place in Parkinson's disease, the explana-

tion being that the extrapyramidal system produces an increase in the sensory impulses, producing the fatigue state. A third, and most complex, process occurs in patients of the neurosis group and those with fatigue complaints that are produced by outside situations in their environment, since in such persons all impulses produce an early fatigue. The authors have made a detailed study of such cases over a five-year period.

They found that in patients with neuroses the complaint of fatigue is generalized, vague, and diffuse. It is often associated with other psychiatric symptoms, and the words "lack of drive," "lack of ambition," "irritation," and "boredom" are commonly used. Their fatigue is usually worse in the morning after a night's sleep and becomes less bothersome during the day.

Further differential tests consisted in the use of neostigmine and in testing the performance of specific muscles, with the following results: 1. In normal persons there is a slight drop in the efficiency of the work done after an injection of neostigmine. 2. In patients with myasthenia gravis there is a dramatic and conspicuous increase in efficiency with the drug. 3. In patients with physical disease there is usually no change with neostigmine, or perhaps an increase in the fatigue. 4. In patients with psychoneuroses there is usually a decrease in work output to a greater degree than in the other two states.

ALPERS, Philadelphia.

INFECTIOUS MONONUCLEOSIS WITH PREDOMINANTLY NEUROLOGIC MANIFESTATIONS: REPORT OF CASE. W. L. HUBLER, A. A. BAILEY, D. C. CAMPBELL, and D. R. MATHIESON, Proc. Staff Meet., Mayo Clin. **26**:313 (Aug. 15) 1951.

Among the neurologic complications of infectious mononucleosis, headache and blurred vision are believed to be the commonest. There is no constant order in which the usual manifestations of the disease and the neurologic symptoms appear. In instances in which the involvement of the nervous system is severe, the changes in the blood picture tend to be delayed. Great variations exist in the duration of the neurologic disability, but rapid recovery is usual. In a review of the subject by Bernstein and Wolff it was stated that recovery was complete in 85% of cases.

In those few instances in which microscopic examination of the nervous system was carried out, a variety of lesions were observed. These included congestion, edema, and mononuclear infiltration of cranial-nerve nuclei and vital medullary centers; focal degenerative changes in the Purkinje cells of the cerebellum, and perivascular cuffing and perivascular and pericellular edema in the cerebral cortex.

Because of the infrequency of convulsions in infectious mononucleosis and the diagnostic difficulties encountered, the authors report the case of a white youth aged 17 whose illness was initiated by headache, exhaustion, and slurred speech, followed in 24 hours by a generalized convulsion. From the indefinite findings in the diagnostic studies, the patient was believed to have obscure encephalitis. His condition gradually improved until, on the ninth day of illness, he again had a seizure. For the first time cervical lymph nodes were palpable. At this time blood smears and heterophile agglutination tests were ordered. On the special blood smear, leucocytoid and atypical lymphocytes were observed. In spite of the absence of pronounced lymphocytosis, this finding was considered characteristic of infectious mononucleosis. The result of the heterophile-agglutination test was positive in a titer of 1:2,048 (normal 1:64). The patient was discharged 12 days later and had no residual disability when checked several months later.

The authors emphasize the important role that the special blood smear and the test for heterophile agglutinins may play in the etiologic diagnosis of an obscure encephalitis or serous meningitis.

Although the diagnosis in this case was established on acceptable criteria, the empirical use of aureomycin and corticotropin was resorted to because of the patient's extremely serious state. The successful outcome was attributed to the expected course of infectious mononucleosis with neurologic manifestations, and not to treatment.

ALPERS, Philadelphia.

ENCEPHALITIS AND ENCEPHALOMYELITIS IN ENGLAND AND WALES DURING THE LAST DECADE. J. G. GREENFIELD, Brain **73**:141 (June) 1950.

Greenfield reports on a survey of virus encephalitis which occurred in England and Wales during 1939. Although encephalitis was rare during this period, the cases tended to fall into four

groups with characteristic clinical syndromes and histological pictures. 1. The acute polioclastic type was of two days' to four weeks' duration. The onset was with headache, malaise, vomiting, and fever, going on to delirium, drowsiness, and unconsciousness. Epileptiform fits were common; paralysis of the cranial nerves and of the limbs was unusual. Examination of the cerebrospinal fluid revealed a moderate increase in cells, chiefly lymphocytes; elevation of the protein; high pressure, which decreased during the course of illness, and normal concentration of glucose and chlorides. Histologically, the inflammation was confined almost wholly to the gray matter; its intensity and location varied greatly. There was usually a meningeal exudate around the larger veins. 2. Acute hemorrhagic leucoencephalitis was characterized clinically by hemiplegia of fairly rapid onset. The cerebrospinal fluid showed a high cell count. The inflammation tended to affect the central parts of the centrum ovale and spread to the crus of the midbrain, the pons, and the cerebellar peduncles. Microscopically, there was an intense exudate of polymorphonuclear leucocytes, especially around the vessels. There were necrosis in the perivascular zones and fibrinous exudate into the vessel walls. The cortex was relatively unaffected. 3. Subacute inclusion-body encephalitis tended to occur in children aged from 4 to 16 years. The symptoms were progressive over a period of weeks, with loss of mentality and decerebrate rigidity later in the illness. Myoclonic jerkings or spasms were common. Death usually occurred seven weeks to six months after appearance of the first symptom. The cerebrospinal fluid characteristically showed a colloidal gold curve characteristic of dementia paralytica. The histological appearance was that of a polioclastic process, with secondary degeneration of the white matter. There were perivascular inflammatory changes and various stages of neuronal degeneration, progressing to complete loss of nerve cells. In many of the degenerated neurons acidophilic hyaline inclusion bodies were seen both in the nucleus and in the cytoplasm. At a later stage the cell might consist only of a rounded inclusion body. 4. Subacute sclerosing encephalitis occurred in children between the ages of 5 and 14 years. The onset was insidious, and involuntary movements were frequent. The cerebrospinal fluid showed only first- and second-zone colloidal gold curves. Histologically, the white and the gray matter were affected to equal degrees. There were diffuse mobilization of the microglia, infiltration of the plasma cells, and diffuse neuroglial sclerosis. Evidence of neuronal damage was comparatively slight.

FRANKEL, Philadelphia.

VISUAL-SPATIAL AGNOSIA ASSOCIATED WITH LESIONS OF THE RIGHT CEREBRAL HEMISPHERE. J. MCFIE, M. F. PIERCY, and O. L. ZANGWILL, Brain **73**:167 (June) 1950.

McFie, Piercy, and Zangwill studied several patients who had apractognosia for spatial articulation, marked by inability to apprehend or reproduce any but the simplest visual-spatial relationships and by restriction and fragmentation of visual perception in its spatial aspects. The disability was correlated with a lesion involving the posterior portions of the right cerebral hemisphere in right-handed persons. In the majority of their patients the defect was associated with the syndrome of neglect of the left side of visual space. In addition to these major defects, and arising in part from them, were difficulties in right-left orientation with regard to external objects, errors in route finding, apraxia for dressing, and constructional anomalies. Several patients displayed, as well, disturbances of oculomotor coordination and control.

FRANKEL, Philadelphia.

POSTPARTUM OPTIC NEURITIS DUE TO MULTIPLE SCLEROSIS. H. W. HAWN, Journal-Lancet **69**:431 (Dec.) 1949.

Hawn says that, according to some observers, optic neuritis is found in 50% of all cases of multiple sclerosis at some stage of the disease. Multiple sclerosis is occasionally first manifested after a normal pregnancy, but pregnancy and some of the other predisposing factors merely activate what was previously a latent or subclinical form of multiple sclerosis. In these women the first symptom of the disease often is sudden onset of blurred vision several months after delivery. The course of the disease and its response to treatment are no different in these cases than in those not associated with pregnancy. During the past two years the author has followed five patients in whom signs and symptoms of multiple sclerosis developed after pregnancy. The histories of two of these patients show that pregnancy may initiate an

attack of optic neuritis in women who previously had no stigma of multiple sclerosis or who had been free of symptoms for a number of years prior to pregnancy and delivery. The questions arise whether a woman who has proved multiple sclerosis should become pregnant and whether interruption of pregnancy is indicated in such women. The author mentions his observations and the opinions of other investigators. He agrees with Fleck, who divides the women in the childbearing age who have multiple sclerosis into two groups. In the group in which there is no progression of the symptoms and little or no disturbance of function or psychic disturbance, he does not advocate either sterilization or interruption of pregnancy. In the second group, in which there is gross disturbance of physical and psychic capacity, he believes that pregnancy should be interrupted and sterilization performed. J. A. M. A.

SUBACUTE SCLEROSING LEUCOENCEPHALITIS WITH INCLUSION BODIES. F. MARTIN, J. MACKEN, and R. HESS, Schweiz. Arch. f. Neurol. u. Psychiat. **66**:217-260, 1950.

Progressive dementia began to develop in a boy aged 7 years 3 months after the onset of whooping cough. Examination revealed aphasia, apraxia, right spastic hemiparesis, with tremors of the right upper extremity, and papilledema. Convulsive seizures and a rather constant elevation of temperature were observed. Eight weeks after the onset of cerebral symptoms, the patient became subject to generalized clonic movements, which were rhythmic in character, accompanied with transient loss of muscular tonus, and synchronous with bursts of theta waves in the electroencephalographic tracings. Electroencephalography also revealed epileptogenic foci, which were subsequently found to correspond to areas of cerebral necrosis. A state of decerebrate rigidity ultimately developed, and the child died of hyperpyrexia four months after the appearance of mental changes.

Anatomically, this case differed from one previously reported under the same title by van Bogaert (*J. Neurol., Neurosurg. & Psychiat.* **8**:101, 1945) by the existence of focal necrosis in both the cerebral cortex and the white matter and the presence of intranuclear and intracytoplasmic inclusion bodies. Focal necrosis and the relatively slight degree of demyelination were most evident in the occipital lobes. The glial and mesenchymovascular reaction was pronounced, especially about the necrotic areas and in the subcortical portions of the white matter. Collections of lymphocytes and plasma cells were observed in the cortex, as well as in the white matter. Degenerative changes involving the basal nuclei were most intense in the pallidum, the dentate nuclei, brain stem, and spinal cord being affected to a less degree. Observations following the inoculation of white mice with spinal fluid and a suspension of brain and spinal cord indicated that the lethal powers of the assumed virus increased with each passage.

DANIELS, Denver.

SPONGIOBLASTOMA OF THE CEREBELLUM. J. A. C. DA SILVA JR., O. AIDAR, and A. M. C. DE ALMEIDA, Arq. neuro-psiquiat. **9**:73 (March) 1951.

A white Brazilian boy aged 13 was admitted to the hospital with the history of an illness of two months' duration, characterized by pains in the neck, followed soon by vomiting. There was definite progression of symptoms to the time of admission. On examination the head seemed to be enlarged; there were unsteadiness in gait and station, with cerebellar ataxia; signs on the right of involvement of the pyramidal tract; bilateral papilledema; diminution of visual acuity; dilation of the pupils, and weakness of the right side of the face. Examination of the spinal fluid showed an initial pressure of 650 mm. when the patient was in the sitting position; there were two cells per cubic millimeter, with a positive Pandy reaction and a negative Wassermann reaction. Roentgenograms of the skull showed increased digitations, separation of the sutures, and calcification in the region of the right posterior fossa. Ventriculographic examination showed pushing of the aqueduct toward the left side, indicating a probable lesion on the right side. An inoperable tumor was observed in the region of the vermis. Autopsy showed a tumor in the region of the vermis, extending into the right hemisphere. In the right hemisphere the tumor was cystic; the cyst did not communicate with the ventricles or the subarachnoid spaces. The histologic diagnosis was spongioblastoma polare.

N. SAVITSKY, New York.

TRAUMATIC GRADENIGO SYNDROME RESULTING FROM GUNSHOT WOUND TO CRANIUM. R. M. FILHO and P. B. MAGALHAES, Arq. neuro-psiquiat. **9**:79 (March) 1951.

A white man aged 21 was shot in the head, the bullet entering the external wall of the left orbit and lodging in the right temporal region. There was no loss of consciousness. The patient suffered severe injury to the left eyeball, which had to be enucleated. After the injury, he noted numbness of the right side of the face and difficulty in chewing on the right side. Neurokeratitis paralytica appeared on the right side six months after injury. Examination five months after the accident showed diminution of sensation of all three branches of the right trigeminal nerve, motor paralysis of the right trigeminal nerve, with deviation of the jaw to the right, and absence of the right corneal reflex. There was no impairment of vibratory sensation on the right side of the face when a C (128 d.v.) fork was used, but definite impairment was evidenced with the C (256 d.v.) fork. There were neurokeratitis paralytica and paralysis of the external rectus on the right side.

No fracture lines could be demonstrated. In the skull the shadow of a metallic substance was observed in the upper surface of the petrous process of the temporal bone. The bullet was found in the right temporal region. The authors state that they have been unable to find a similar case in the literature.

N. SAVITSKY, New York.

News and Comment

THE AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY, INC.

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THE AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY

The American Board of Psychiatry and Neurology, Inc., will hold its first examination this year on June 13 and 14 in Chicago. The deadline for receipt of applications for this examination is March 15. There will be an examination on Dec. 15 and 16, 1952, in New York. The deadline for receipt of applications for this examination is September 15. The number of candidates for each examination must be limited. Early application is advised. Communications may be addressed to the Secretary, David A. Boyd Jr., M.D., 102-110 Second Ave., S.W., Washington, D. C.

NATIONAL TRAINING LABORATORY IN GROUP DEVELOPMENT

After five years of pioneering research and experience in the relatively new field of training leaders in the skills and understanding necessary for the development of effective groups, the National Training Laboratory in Group Development will hold an expanded four-week summer laboratory session at Gould Academy, Bethel, Maine, from June 22 through July 18.

During the past five years three-week laboratory sessions have been held. The four-week laboratory plan results from increased knowledge of group development and additional knowledge about methods of training in human relations.

Approximately 100 applicants will be accepted for this session. Persons involved in problems of working with groups in a training, consultant, or leadership capacity in any field are invited to apply.

The purpose of the training program is to sensitize leaders in all fields to the existence and nature of the dynamic forces operating in the small group. This is organized so that each

trainee group, of 15 to 20 persons, is enabled to use its own experience as a laboratory example of group development. Group skills of analysis and leadership are practiced through the use of role-playing and observer techniques. Concentrated clinics give training in the skills of the consultant and the trainer in human-relations skills. There is also opportunity to explore the role of the group in the larger social environment in which it exists.

The laboratory research program in group behavior and training methods is an important part of the training, and the use of research tools which are within the range of the laboratory training program is incorporated into the curriculum.

The National Training Laboratory in Group Development is sponsored by the Division of Adult Education Service of the National Education Association and the Research Center for Group Dynamics of the University of Michigan, with the cooperation of the faculty members of the Universities of Chicago, Illinois, and California; Ohio State University; Antioch College; Teachers College, Columbia University, and other educational institutions. Its year-round research and consultation program is supported by a grant from the Carnegie Corporation of New York. For further information, write the National Training Laboratory in Group Development, 1201 16th St., N.W., Washington 6, D. C.

COMMISSIONS IN MEDICINE, UNITED STATES AIR FORCE

The United States Air Force has announced a program whereby commissions will be offered to young men and women practicing in all fields of medicine and in all allied specialized vocations.

The list of vocations includes doctors of preventive medicine, gastroenterologists, obstetricians, gynecologists, allergists, anesthesiologists, ophthalmologists, otorhinolaryngologists, neurologists, internists, general and orthopedic surgeons, radiologists, oral surgeons, periodontists, prosthodontists, medical supply and medical equipment maintenance specialists, sanitary engineers, clinical laboratory technicians, general duty and anesthetist nurses, dietitians, and physical therapists.

Each classification has a different set of requirements for each grade from second lieutenant through the higher grades. The First Air Force has set up clerical facilities for promptly answering all queries concerning these commissions. Inquiries should be directed to the Air Surgeon, Headquarters, First Air Force, Mitchell Air Force Base, New York.

WORK CONFERENCES IN MENTAL HEALTH RESEARCH

A series of interdisciplinary work conferences in mental health research is being conducted under a grant from the National Institute of Mental Health. The project was established because of the need, expressed by workers in the field, for an exchange of thinking and experience regarding methods and problems of interdisciplinary collaboration in mental health research. The general objective, as stated by the advisory committee is "to stimulate research in mental health through the collaborative study of how the concepts and methods of relevant disciplines may be better understood and used."

An advisory committee, with Ronald Lippitt as chairman, provides over-all guidance for the conference series. Jacob E. Finesinger is the representative of psychiatry, and Harold G. Wolff, of neurology. Other members are David Shakow (psychology), Margaret Mead (anthropology), and William Fielding Ogburn (sociology). Ex officio members include Leland P. Bradford, director of the National Training Laboratory for Group Development, and John A. Clausen and John C. Eberhart, both of the National Institute of Mental Health. Margaret Barron Luszki is the project coordinator. Offices of the project are located at the National Institute Training Laboratory for Group Development, 1201 16th Street, N.W., Washington 6, D. C.

The first conference of the series, held in conjunction with the meeting of the American Anthropological Association, was concerned with an analysis of specific interdisciplinary research projects. The conference found that in the development of research plans there had been relatively little anticipation of the problems actually encountered in the research, and as a result, in many instances, projects had been beset with unexpected, yet common, difficulties without any established pattern for handling them. Through its efforts to analyze and outline the components and processes in interdisciplinary research, a number of stimulating lines of inquiry were developed for the consideration of later conferences, one of which will be held May 9 through 11 under the leadership of Jacob Finesinger, Eugene Ferris, and David Shakow.

Highlights of this conference which are of particular interest to psychiatrists will be discussed on May 13 at the evening meeting of the American Psychiatric Association, in Atlantic City, N. J.

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